UNIVERSIDADE D
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Remote Management of Diabetic Patients

Dissertação no âmbito do Mestrado em Engenharia Biomédica orientada pelo Professor Doutor Jorge Henriques e pelo Professor Doutor Paulo de Carvalho apresentada à Faculdade de Ciências e Tecnologia da Universidade de Coimbra.

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Resumo

A diabetes mellitus tipo 2 é a forma mais comum dos três principais tipos de diabetes. Caracteriza-se por ser uma doença crónica que afeta a capacidade do organismo controlar os níveis de glicose no sangue com consequências significativas a curto e longo prazo. Os recentes avanços tecnológicos na área da diabetes, tais como os sistemas de monitorização contínua da glicose, fornecem fontes fiáveis de dados. Este tipo de dispositivos quando acoplados a aplicações smartphone que ajudam e encorajam mudanças no estilo de vida dos pacientes permitem uma maior proximidade com a doença e, consequentemente, melhoram o controlo glicémico, prevenindo potenciais episódios perigosos para a saúde dos indivíduos com esta patologia.

A presente tese faz parte do projeto financiado intitulado "POWER - Empowering a digital future". Sendo que, de vários subprojetos integrados, esta insere-se no âmbito da Assisted Living e e-Health. O objetivo é investigar metodologias de inteligência artificial e desenvolver uma plataforma algorítmica para a análise e previsão de sinais fisiológicos, bem como a sua utilização na gestão da diabetes. Portanto, é possível dividir os objetivos desta tese em dois módulos. Um correspondente à previsão dos níveis de glicose para pacientes com diabetes tipo 2, e o outro relativo ao fornecimento de recomendações que incidam sobre os hábitos de vida dos mesmos, utilizando as previsões feitas pelo modulo anterior como suporte.

Relativamente ao módulo da previsão, compararam-se diferentes modelos tais como Autoregressive Integrated Moving Average (ARIMA), Case-based reasoning (CBR), Recurrent Neural Network (RNN), Long Short-Term Memory (LSTM), Gated Recurrent Unit (GRU) e Jump Neural Network (JNN). Através de um compromisso entre o desempenho do modelo e a complexidade computacional, o modelo RNN foi escolhido como o modelo final. Verificou-se que esta implementação pode ser utilizada para obter resultados satisfatórios no horizonte de previsão (PH) de 2h e 4h. Para a sua utilização num horizonte de 12h, deve observa-se que os resultados não serão os mais adequados. As experiências foram realizadas utilizando os dados

de 10 indivíduos registados em condições de vida livre. Destes, utilizámos 3 pacientes, escolhidos aleatoriamente, no conjunto de dados para testar os algoritmos implementados. Os resultados globais para o modelo RNN foram: 34,82 mg/dL para o erro quadrático médio (RMSE) e 18,33% para o erro percentual médio absoluto (MAPE) (PH=2h); 46,59 mg/dL para RMSE e 24,35% para MAPE (PH=4h); 50,19 mg/dL para RMSE e 27,74% para MAPE (PH=12h). Uma das etapas futuras deste projeto consiste em validar os modelos implementados num conjunto de dados recolhidos e fornecidos pelo Centro Hospitalar e Universitário de Coimbra (CHUC). Com estes dados, pretende-se incorporar mais algumas características para além do registo dos valores de glicose, tais como a ingestão de hidratos de carbono e o nível de atividade física. Uma contribuição deste trabalho é o desenvolvimento de um modelo de previsão para pacientes com diabetes tipo 2, cuja existência na literatura é escassa. São necessários mais estudos nesta área para compreender e melhorar os modelos para estes pacientes. Deverão ser feitos mais estudos para identificar quais os horizontes de previsão mais úteis para os pacientes do tipo 2.

Já no módulo da recomendação, desenvolveu-se um sistema de recomendação baseado em conhecimento, implementado através de regras extraídas de diretrizes fornecidas pelas principais associações internacionais de diabetes. Todas as regras desenvolvidas foram testadas através da criação de cenários hipotéticos, a fim de verificar que eram sugeridas quando necessário e de forma correta. O trabalho futuro consiste na validação e complementaridade destas regras por parte de uma equipa de endocrinologistas dos CHUC, principalmente no desenvolvimento de novas regras que utilizem os valores obtidos pelo módulo de previsão como input, de modo a criar regras mais personalizadas. A existência da previsão, além de alertar o paciente para a existência de picos de glicose potencialmente perigosos, fornecerá esses valores ao módulo de recomendação. Assim, com base nos futuros valores de glicose previstos, poderão ser sugeridas modificações nas ações do quotidiano dos pacientes. Estas, quando tomadas, devem evitar que os picos previstos sejam atingidos e, assim, ajudar a gerir o valor da glicose na gama saudável.

As fases futuras deste projeto, que contarão com a parceria da Altice Labs e do CHUC, serão cruciais para validar e melhorar os módulos desenvolvidos. Uma vez concluídas, a API implementada na plataforma de gestão remota para pacientes diabéticos SmartAL da Altice será atualizada.

Palavras-chave: Diabetes mellitus tipo 2, Previsão dos níveis de glicose, Sistema de recomendação, Doenças crónicas, Telemonitorização.

Abstract

Type 2 diabetes mellitus is the most common form of the three main types of diabetes. It is a chronic disease affecting the body's ability to control blood glucose levels with significant short and long-term consequences. Recent technological advances in the field of diabetes, such as Continuous Monitoring Devices (CGMs), provide reliable sources of blood glucose data. These types of devices when coupled with smartphone applications that help and encourage lifestyle changes in patients, allow a greater proximity to the disease and consequently improve glycemic control, preventing potentially dangerous episodes to the health of individuals with this pathology.

This thesis is part of the funded project entitled "POWER - Empowering a digital future". Of several integrated subprojects, this one falls under the scope of Assisted Living and e-Health. The goal is to investigate artificial intelligence methodologies and develop an algorithmic platform for the analysis and prediction of physiological signals, as well as its use in diabetes management. Therefore, it is possible to divide the objectives of this thesis into two modules. One corresponding to the prediction of glucose levels for patients with type 2 diabetes, and the other related to the provision of recommendations that focus on their lifestyle habits, using the predictions made by the previous module as support.

Regarding the forecasting module, different models such as ARIMA, CBR, RNN, LSTM, GRU and JNN were compared. Through a trade-off between model performance and computational complexity, the RNN model was chosen as the final model. It was found that this implementation can be used to obtain satisfactory results in the Prediction Horizon (PH) of 2h and 4h. For its use in 12h horizon, it should be observed that the results will not be the most adequate. The experiments were performed using data from 10 individuals recorded in free-living conditions. Of these, we used 3 randomly chosen patients in the data set to test the implemented algorithms. The overall results for the RNN model were: 34.82 mg/dL for

Root Mean Square Error (RMSE) and 18.33% for Mean Absolute Percentage Error (MAPE) (PH=2h); 46.59 mg/dL for RMSE and 24.35% for MAPE (PH=4h); 50.19 mg/dL for RMSE and 27.74% for MAPE (PH=12h). One of the future stages of this project consists in validating the models implemented in a set of data collected and provided by the Coimbra Hospital and University Centre (CHUC). With these data, it is intended to incorporate some more features in addition to the recording of glucose values, such as carbohydrate intake and level of physical activity. A contribution of this work is the development of a prediction model for patients with type 2 diabetes, whose existence in the literature is scarce. More studies are needed in this area to understand and improve models for these patients. Further studies should be conducted to identify which prediction horizons are most useful for type 2 patients.

As for the recommendation module, a knowledge-based recommendation system was developed and implemented using rules extracted from guidelines provided by major international diabetes associations. All developed rules were tested through the creation of hypothetical scenarios, in order to verify that they were suggested when necessary and correctly. Future work consists in the validation and complementarity of these rules by a team of endocrinologists. Mainly, in the development of new rules that use the values obtained by the prediction module as input, in order to create more personalized rules. The existence of the prediction, besides alerting the patient to potentially dangerous glucose peaks, will provide these values to the recommendation module. Thus, based on the predicted future glucose values, modifications to the patients' everyday actions can be suggested. These, when taken, should prevent the predicted peaks from being reached and thus help manage the glucose value in the healthy range.

The future stages of this project, which will count on the partnership of Altice Labs and CHUC, will be crucial in validating and improving the modules developed. When completed, the API implemented in Altice's SmartAL remote management platform for diabetic patients will be updated.

Keywords: Type 2 diabetes mellitus, Glucose level prediction, Recommendation system, Chronic diseases, Telemonitoring.

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List of Abbreviations

AI Artificial Intelligence. 3, 15, 22, 34
ANN Artificial Neural Network. 16, 30, 31
APDP Associação Protetora dos Diabéticos de Portugal. 4, 39, 40, 54
API Application Programming Interface. 38, 43, 48, 49, 67
AR Autoregressive. 30, 33
ARIMA Autoregressive Integrated Moving Average. iv, vi, 14, 31, 43, 54, 55, 56, 59

BG Blood Glucose. 2, 4, 26, 27, 28, 30, 31, 36, 60
BiLSTM Bidirectional Long Short-Term Memory. 31, 33
BMI Body Mass Index. 28, 30, 35, 40, 62, 64, 85

CB Content-Based. 22
CBR Case-based reasoning. iv, vi, xi, 14, 15, 43, 44, 53, 54, 56, 59
CEGA Clarke Error Grid. 45, 46, 57, 59
CF Collaborative Filtering. 22
CGM Continuous Monitoring Device. vi, xi, 1, 2, 4, 13, 14, 15, 26, 27, 28, 30, 31, 32, 39, 40, 41, 42, 48, 49, 50, 51, 53, 61, 66
CHUC Coimbra Hospital and University Centre. vii, 3, 63, 67
CISUC Center of Informatics and Systems of the University of Coimbra. 3

DEI Department of Informatics Engineering. 3
DM Diabetes Mellitus. 1, 9, 11, 29

FCTUC Faculty of Sciences and Technology of the University of Coimbra. 3
FFNN Feed-Forward Neural Network. x, 16, 17, 18, 30, 33

GRU Gated Recurrent Unit. iv, vi, x, xi, 14, 19, 20, 21, 22, 32, 33, 43, 45, 54, 56

HbA1c Hemoglobin A1c. 3, 10, 12, 25, 27, 28, 29, 30, 34, 36, 40
HRS Hybrid Recommender systems. 22

JNN Jump Neural Network. iv, vi, x, 14, 18, 31, 33, 43, 44, 54, 56, 59

KB Knowledge-Based. 22
KBRS Knowledge-Based Recommendation System. 4, 22, 23, 38, 47, 61

LR Linear Regression. 44, 53
LSTM Long Short-Term Memory. iv, vi, x, xi, 14, 19, 20, 21, 22, 31, 32, 33, 43, 45, 54, 56, 59

MAE Mean Absolute Error. 32
MAPE Mean Absolute Percentage Error. vii, xi, 32, 45, 54, 55, 56, 57, 66
MARD Mean Absolute Relative Difference. 26, 27
ML Machine Learning. 3, 4, 37

NN Neural Network. 18, 31

PH Prediction Horizon. vi, vii, xi, 13, 14, 30, 31, 32, 33, 38, 42, 43, 48, 50, 52, 53, 55, 56, 57, 59, 60, 61, 64

RBS Rule-based system. 23, 47, 49
RMSE Root Mean Square Error. vii, xi, 30, 31, 32, 33, 45, 54, 55, 56, 57, 66
RNN Recurrent Neural Network. iv, vi, ix, x, xi, 14, 19, 20, 22, 32, 33, 43, 45, 53, 54, 56, 58, 59, 60, 66, 81, 82, 83
RS Recommendation system. 22, 32, 34

SMBG Self-Monitoring of Blood Glucose. 26, 27
SVR Support Vector Regression. 31

T1DM Type 1 Diabetes Mellitus. 8, 11, 27, 30, 31, 33, 49, 50
T2DM Type 2 Diabetes Mellitus. 1, 2, 5, 6, 8, 9, 10, 11, 25, 27, 28, 29, 30, 33, 36, 40, 42, 50, 61, 66

1

Introduction

1.1 Motivation

Diabetes Mellitus (DM) is a chronic disorder that affects the body's ability to control blood glucose levels with significant short and long-term consequences. It is estimated that in 2018 the prevalence of diabetes in Portugal between the ages of 20 and 79 years was 13.6%. This means that more than 1 million Portuguese people in this age group have diabetes, of which 56% live with the disease and 44% have undiagnosed diabetes [1].

Patients with diabetes, to maintain their blood glucose level within healthy limits, must follow a set of behavioral actions, such as following a food plan, practicing sufficient physical activity, and taking medication [2, 3]. These lifestyle changes in patients are essential to achieve therapeutic goals, especially for patients with Type 2 Diabetes Mellitus (T2DM). In fact, some studies show that these interventions are more effective than pharmacological interventions and can even prevent cases of T2DM [3, 4].

The current paradigm of health systems is mainly focused on the immediate care of acute illnesses. With the high incidence of chronic diseases, it is essential to shift this focus to prevention and management. Therefore, remote health is employed to provide patients a closer follow-up with the necessary frequency [5]. In addition, this has the potential to provide a reduction in costs and occupancy of health establishments [5, 6].

Remote health includes several approaches (telehealth, remote monitoring, mobile applications, etc.), all of which mean observing patients outside the clinic using technologies [6]. For type 2 diabetes, there are several solutions on the market, such as Continuous Monitoring Devices (CGMs) and mobile applications with several functionalities, from analyzing CGM data, alerting of dangerous episodes, medication intake reminders, incentive changes in the patients' lifestyle, among others [7]. Studies indicate that mobile health (mHealth) interventions show clinical effective-

ness in the prevention and management of T2DM [8, 9]. So, the development of an algorithm that uses CGM data, predicts future glucose values, and, through them, makes recommendations about the patients' lifestyle (with a mHealth interface) will help doctors and patients manage their disease and prevent dangerous episodes from occurring in their lives.

1.2 Contextualization

Type 2 diabetes mellitus is the most common of the three main types of diabetes. It results from deficient secretion, insulin resistance, or a combination of both and is characterized by dysregulation of carbohydrate, lipid, and protein metabolism [4].

This pathology has raised globally in the last three decades, mainly in the most industrialized countries. Subsequently to increasing urbanization, population aging, obesity, unhealthy eating habits, and sedentary lifestyles [2, 4, 10, 11]. Affecting all age groups, type 2 diabetes results in heightened mortality, morbidity, and a significant reduction in the quality of life of individuals dealing with this disease. Mainly increasing cardiovascular disease, end-stage renal disease, retinopathy, and neuropathy [2, 4, 10, 11]. To avoid this situation and to achieve moderate blood glucose levels, patients need to take pharmacological treatment and adjust their lifestyle [2, 10]. These changes in the patients' lifestyle are essential in managing and preventing type 2 diabetes and constitute the first approach to their treatment [4]. Some studies show that these adjustments if made persistently, become more effective than taking medication [4].

Since this disease is highly influenced by the patient's day-to-day behaviors, it is extremely important that the patient can anticipate dangerous events to adapt their actions. With the growing development of technologies and the increase in internet access, the field of telemedicine is becoming more and more relevant in the detection and management of T2DM [5].

As mentioned before, in patients with this pathology there is a critical need for personal monitoring and control of the Blood Glucose (BG) levels [12], for which there are sensors and devices capable of extracting and recording those values through remote monitoring. Blood glucose monitoring has been revolutionized in the last few decades by CGM sensors, which are temporary minimally invasive sensors inserted in subcutaneous tissue (usually in the abdomen or in the arm). These provide BG readings every 1 to 5 minutes, with a large range of functionalities, such as alarms for imminent hyperglycemic or hypoglycemic episodes, arrows depicting current glucose level change direction, remote monitoring and wireless communica-

tion that allows data sharing with caregivers and real-time information visualization via a portable receiver or a smartphone.

Currently, there are intelligent computational techniques, such as Machine Learning (ML) and Artificial Intelligence (AI), that analyze and extract timely information for patients through the acquired data [13]. These algorithms are particularly useful in diagnosing the pathology [13], predicting population risk stratification, improving decision-making and [14] self-management. These algorithms are often found in mobile apps, websites, etc. Some studies show that this combination of technologies (monitoring devices with intelligent algorithms) can contribute to the decrease in the value of Hemoglobin A1c (HbA1c) and improves glycemic control, self-efficacy, and self-care activities [14–16].

1.3 Goals

The present thesis was part of the ongoing funded project entitled "POWER - Empowering a digital future". This project aims to create an innovative portfolio of products and services, mostly based on cloud and cognitive technologies. Through a strong research and development effort aligned around five strategic technological transformation vectors: 5G networks, Edge/Cloud computing continuum, data-driven technologies, business models, and AI.

This project is divided into five subprojects, and this thesis is part of subproject 4: Future Services. Therefore, within this theme, Altice Labs and the University of Coimbra (Faculty of Sciences and Technology of the University of Coimbra (FCTUC)/Department of Informatics Engineering (DEI)), together with the collaboration of the Coimbra Hospital and University Centre (CHUC), are working on the scope of Assisted Living and e-Health. The purpose is to investigate AI methodologies and develop an algorithmic platform for the analysis and prediction of physiological signals, and their use in the management of diabetes. The development of this thesis took place at the Center of Informatics and Systems of the University of Coimbra (CISUC).

Therefore, we can divide the goals of this thesis into two modules. One corresponding to the prediction of glucose values for patients with type 2 diabetes, and the other to the provision of recommendations that focus on the patients' lifestyle habits:

1. Prediction module
2. Recommendation module

To achieve the first goal, algorithms will be implemented using only previous

blood glucose values measured using a CGM device, which provides periodic BG readings, as mentioned earlier. For this purpose, some secondary goals will be established: find the model with the best results, comparing traditional methods and ML methods; validate the performance of the model using real patient data from a dataset provided by Associação Protetora dos Diabéticos de Portugal (APDP); compare the results using different metrics.

For the second module, a recommendation model will be developed using a Knowledge-Based Recommendation System (KBRS). Knowledge will be extracted from guidelines developed by major international institutions related to the pathology. These guidelines will be transformed into a set of rules which are then adopted to create personalized recommendations for the users. This customization will be achieved by using the prediction module to support the recommendations. The rules developed will be validated and complemented by the clinical knowledge of a team of endocrinologists. Thus, there will be a validation with confidence and clinical relevance of the chosen recommendations.

1.4 Structure

In addition to this introduction, this document has five more chapters. In Chapter 2, the physiological and technical background is presented, where the concepts necessary for a better understanding of the work developed in this study are exposed. Chapter 3 discusses the state of the art of both the models used to predict glucose levels and the existing recommendation rule engines. Then, in Chapter 4, the methodologies used to implement the models for both modules are represented. For the prediction the dataset used and how the data from it was pre-processed and framed for use in the models is described. How the models were optimized and what evaluation metrics were used were also described. Regarding the recommendation system, it is explained how the knowledge was obtained and what strategy was adopted to generate the rules. Subsequently, Chapter 5 describes and discusses the results of the experiments. Finally, Chapter 6 presents the main conclusions of the work. The document also has a set of appendices that contain complementary information to that written during the different chapters.

2

Background

This chapter aims to explain the main concepts required to understand this thesis and is organized in two sections: physiological and technical background. Section 2.1 intends to clarify some concepts about the disease and expose the consensus reached on the influence of lifestyles in the treatment of diabetes. Section 2.2 explains the main ideas and techniques that are used in the development of both the prediction and recommendation modules.

2.1 Physiological background

2.1.1 Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance or a combination of both [17, 18]. Insulin is the main anabolic hormone of the body produced by β-cells of the pancreatic islets. Metabolic abnormalities in carbohydrates, lipids, and proteins are caused by inadequate insulin levels to produce an adequate response and/or insulin resistance of target tissues, primarily skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes [17]. This pathology is mainly divided into three types [18–21]:

1. **Type 1 diabetes**: autoimmune disease, also known as insulin-dependent diabetes, is brought on by the body attacking the pancreas. Absolute insulin, including latent autoimmune diabetes in adulthood, results from the destruction of β-cells. It accounts for 5 to 10% of people with diabetes, with a higher prevalence in kids and teens.
2. **Type 2 diabetes**: also known as non-insulin-dependent diabetes, accounts for 90 to 95% of diabetes cases. Due to insulin resistance, reduced insulin synthesis, and dysfunctional pancreatic β-cells, it is characterized by insulin insensitivity. Having relatives with Type 2 Diabetes Mellitus (T2DM) (espe-

cially those in the first degree) significantly raises one's likelihood of acquiring the disease, indicating that type 2 diabetes is strongly inherited genetically. Aging, diets rich in fat, and a sedentary lifestyle are additional risk factors for T2DM.

3. **Gestational diabetes**: pregnancy-related glucose intolerance condition that is often identified in the second or third trimester. The risk of developing this illness is increased by characteristics such advanced mother age, ethnicity, a history of gestational diabetes, and a family history of T2DM.

Other specific types of diabetes include monogenic diabetes syndromes (like neonatal diabetes and maturity-onset diabetes of the young [MODY]), exocrine pancreas diseases (like cystic fibrosis), and drug- or chemical-induced diabetes (as it occurs during treatment for HIV/AIDS or after organ transplantation)[19, 20]. Prediabetes is a condition when blood glucose levels are higher than usual but not high enough to be diagnosed as diabetes. Patients who have this syndrome are more likely to develop T2DM, but with the right lifestyle changes, the pathology can be avoided or delayed [3, 18, 20].

Diabetes often remains undetected, sometimes due to a lack of knowledge about the disease symptoms, to low health-seeking behavior, like lack of regular health check-ups, or because patients are asymptomatic, especially those with type 2 diabetes during the first years of the disease. [18, 22]. Uncontrolled diabetes can cause substantial long-term damage to many organs and bodily functions, such as the kidneys, heart, nerves, blood vessels, and eyes. It can also cause stupor, coma, and, if left untreated, death from ketoacidosis or a rare form of nonketotic hyperosmolar syndrome [4, 11, 17]. Therefore, early illness identification enables people at risk to take preventative measures to halt the disease's course and enhance their quality of life.

2.1.2 Glucose regulation mechanisms

In order to enhance current therapies and drugs and create novel strategies, it is essential to fully comprehend the processes that control blood glucose levels. A highly sophisticated network of hormones and neuropeptides, mostly secreted by the brain, pancreas, liver, intestine, as well as adipose and muscle tissue, is responsible for this glycemic regulation [23].

The pancreas, which releases many digestive enzymes and pancreatic hormones, including insulin and glucagon, is the primary regulator of this system. These two hormones work in opposition to one another to maintain a range of blood glucose

levels between 4 and 6 mm (72 and 108 mg/dL) and achieve glycemic homeostasis [23].

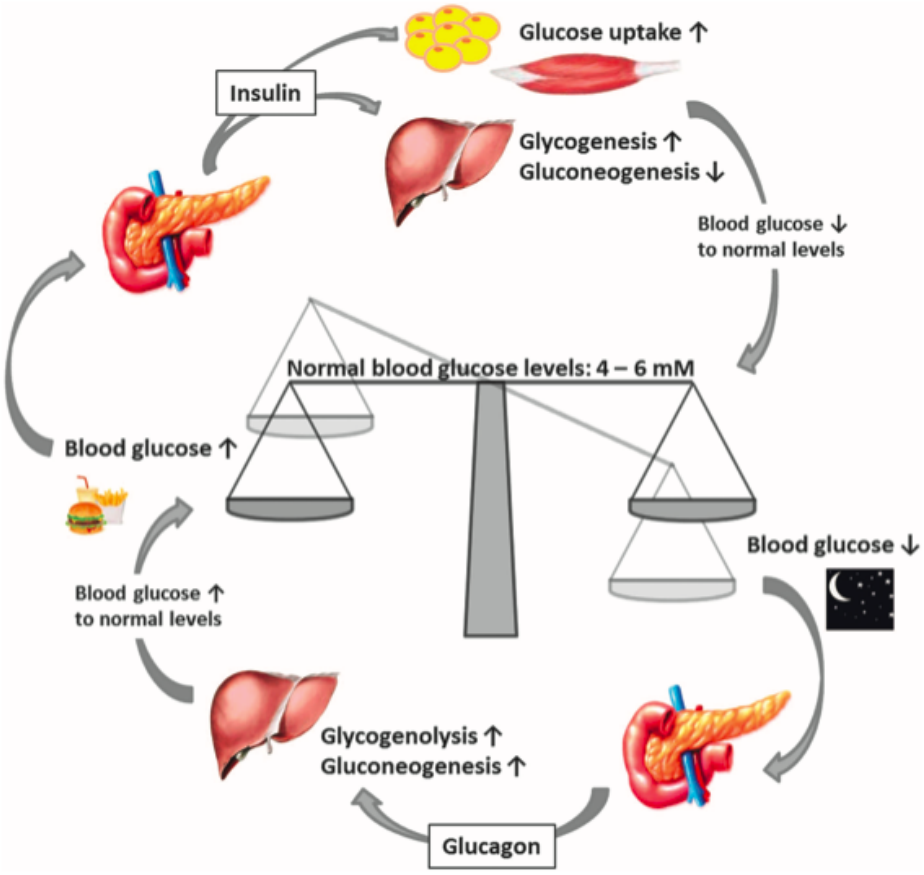


Figure 2.1: Maintenance of blood glucose levels by glucagon and insulin. From [23].

On the one hand, glucagon is released into the bloodstream when blood glucose levels are decreased, such as during sleep or in between meals. It encourages hepatic glycogenolysis, a process in which the liver produces glucose by liberating it from glycogen stores to power other organs like the brain, red blood cells, and muscles [24]. This procedure is especially important when there are protracted fasting intervals. In order to raise endogenous blood glucose levels during extended fasting, glucagon also encourages hepatic and renal gluconeogenesis [23, 24].

On the other hand, when blood glucose levels are elevated, as they are after meals, insulin is produced. Through a receptor in adipose tissue, this hormone allows for the uptake of glucose by these tissues, lowering its concentration in the bloodstream. It also promotes lipogenesis (the synthesis of fatty acids and triglycerides, which will later be stored in the liver and adipose tissue) and glycogenesis (the addition of glucose molecules to the glycogen chain) [4, 23].

Therefore it becomes evident that the pancreas, liver and kidneys play a crucial role in regulating blood sugar levels. A problem between the functional iterations of all relevant components can result in impairments in insulin secretion and/or sensitivity, which can cause disorders like T2DM [18, 23].

2.1.3 Treatment and management of diabetes

As previously noted, if this disease is not controlled, it can lead to several health issues. Patients must simultaneously change their lifestyle and undergo pharmaceutical therapy to avoid this condition and attain moderate blood glucose levels [2, 10, 18].

Pharmacological agents

Since individuals with Type 1 Diabetes Mellitus (T1DM) are distinguished by a lack of endogenous insulin production and autoimmune destruction of β-cells in the pancreas, insulin injection is the cornerstone of treatment for these patients. Invasive delivery methods, including diabetes syringes, glucose sensor insulin infusion pumps, supersonic injectors, and pens, can be used to provide external insulin [25, 26]. Similar to how endogenously released insulin travels via the liver first, a fully physiological exogenous insulin treatment should be delivered in this way. Since the pancreas continuously secretes a tiny quantity of insulin and produces bigger amounts in reaction to a carbohydrate-rich meal, the present insulin delivery is made to more nearly resemble the physiological scenario seen in a healthy individual [26].

However, the exclusive focus on exogenous insulin turns out to be insufficient to address all the issues related to the illness, leaving patients vulnerable to severe hypoglycemic episodes like, a lifetime need on exogenous insulin, insulin resistance, mild obesity, and psychological issues [25]. The creation of a real artificial pancreas has advanced thanks to technological advancements that enable the widespread adoption of smaller, better insulin pumps and continuous glucose monitoring. Until a biological medicine is established, the artificial pancreas is anticipated to enhance care and lower consequences and comorbidities [26].

There are several oral and injectable treatments available to people with T2DM to address the disease [10]. For the majority of patients, metformin is the first drug of choice from a pharmacological standpoint [10, 27, 28], while the other alternative therapies must be researched and administered on an individual level, taking into consideration the patient's features and condition. It is important to empha-

size that most type 2 diabetes guidelines recommend starting treatment based on lifestyle changes, particularly nutritional changes and physical activity, before starting pharmacotherapy [4, 29].

Non-pharmacological agents

It is vital to incorporate lifestyle modifications into the treatment/management for both forms of diabetes, but particularly for those with T2DM [4, 30]. These adjustments include self-management education and support, medical nutrition therapy, physical activity and psychosocial care [30].

Large-scale clinical studies have demonstrated that intensive lifestyle treatments are more successful than pharmaceutical therapies in reducing the prevalence of Diabetes Mellitus (DM) by 58% when compared to control groups [4]. Other important clinical studies, like the Diabetes Prevention Program in Multiethnic Americans, the Finnish Diabetes Prevention Study, and the Da Qing IGT and Diabetes Study in China, have shown that a significant number of T2DM cases can be avoided by modifying their lifestyle, by developing a balanced eating plan and boosting physical exercise [4].

These modifications, however, take time and can be challenging since people need to learn about their condition and how they can promote health and avoid consequences. These changes may also be hampered by other variables, such as a lack of motivation (which may occasionally be brought on by symptoms of the disease, such as fatigue) and the absence of social support. Therefore, it is crucial for people with DM to have a strong support system and to be well-informed about their illness [2].

- **Nutrition therapy and weight control**

  The need to maintain weight, plan meals, and adhere to a chronic diet are some of the most challenging aspects for DM patients [29, 30]. In obese persons with diabetes, losing weight significantly improves blood pressure, lipid levels, and glycemic control [29, 31]. Since this pathology covers a very diverse set of individuals, due to personal preferences, culture, comorbidities, socioeconomic settings, and other considerations, there is no model diet that is suitable for everyone with this illness [29, 31].

  Despite generating discord between scientists and health experts, some consensus has already been made, such as the suggestion that health professionals who treat patients of this type should base their recommendations on diets that encourage the consumption of nonstarchy vegetables, fruits, whole grains,

vegetables, nuts, dairy products (such as yogurt, but with some caution), and choosing whole foods over processed foods [29–31]. In addition, it is advised to limit or avoid the consumption of processed red meats, refined carbohydrates, and sugars (particularly those found in sugar-sweetened beverages) for the prevention and control of type 2 diabetes, but again with some cautions [29–31].

Reducing carbohydrate intake for patients with this pathology has been shown to be the greatest evidence for improving blood glucose, since these are the only food constituents that directly increase blood glucose [31]. Therefore, a low- or very low-carbohydrate diet is an option for people with T2DM who are unable to achieve their glycemic objectives or who wish to cut back on pharmaceutical therapy [29–31].

Even though there has already been considerable success in this area of nutritional study and certain formulations of dietary recommendations have been made, there are still a number of contentious and ambiguous problems that require further research to be clarified. Nuts, fruits, seafood, vegetable oils, low-fat vs high-fat dairy, and the quantity and quality of the diet are the main factors. It is still necessary to comprehend the etiological elements that link diet, diabetes, and associated consequences in various geographic and racial contexts [29, 31].

- **Physical activity and exercise**

  Exercise provides many general advantages for everyone, but especially for those with diabetes. Numerous studies have shown that progressive aerobic and resistance training, when performed alone or in various combinations (without dietary modification), has multiple positive effects on body composition (such as a reduction in total body fat and visceral adipose tissue), cardiometabolic risk factors (such as an improved blood lipid profile and blood pressure), and particularly on the mechanisms that control glucose homeostasis (such as improved insulin sensitivity and decreased Hemoglobin A1c (HbA1c)) [3, 30, 32, 33]. The challenges of glycemic control via physical activity and exercise planning, like those of nutrition, must be tailored to each person's unique requirements since they depend on the type of diabetes, the kind of activity, and the existence of morbidities.

  It is strongly advised that people with diabetes avoid being sedentary, or engaging in activities with very little energy expenditure (such as watching TV, sitting at the computer, etc.). This kind of extended behavior, which

is reflected in poor glycemic control and pooled metabolic risk, is linked to higher mortality and morbidity rates [3, 30, 34].

Through insulin-independent processes, aerobic exercise immediately boosts muscle glucose absorption by a factor of up to five [3]. If exercise is prolonged, it is associated with muscle glycogen repletion and glucose uptake after exercise stays high through insulin-independent ($\sim$ 2 h) and insulin-dependent (up to 48 h) mechanisms [3, 33].

Some consensuses were established for patients with T2DM regarding the duration and type of activity to be performed. In order to improve insulin action, it is advised that individuals exercise regularly, or at the very least refrain from going more than two days without exercising. For the best effects on glucose control and overall health, patients should ideally combine aerobic and resistance training. To prevent or postpone the onset of type 2 diabetes in high-risk groups and those with prediabetes, structured lifestyle treatments that involve at least 150 minutes per week of physical activity and dietary adjustments that lead to a 5–7% weight reduction are advised. The same physical activity targets set for young people in general should be advocated for children and teenagers with T2DM [3, 30, 34, 35].

Patients with T1DM have extremely variable glycemic responses due to the type and duration of exercise, and each requires different adjustments. It is essential to adjust supplemental carbohydrate intake and/or insulin decrease during and after exercise in order to maintain glycemic balance. Frequent monitoring of glucose levels is necessary to make these modifications more correctly [3, 30].

- **Psychological background**

  Patients with chronic diseases typically experience increased levels of anxiety and stress as a result of having to adapt to their condition and through a number of lifestyle modifications [36, 37]. For patients with DM, these emotions include suffering related to self-care, adherence to the nutritional and physical program, and adaptation to the comorbidities associated with the pathology, since the treatment of this disease affects all aspects of the patient's life, including occupation, leisure and family, and social life [36, 37].

  In addition to therapy and maintenance, there is a 25% chance of acquiring depression after receiving a diabetes diagnosis [38]. These patients regularly face anxiety and stress about experiencing episodes of hypoglycemia or hyperglycemia [38] and worry about keeping their blood glucose levels steady, both

of which raise the risk of depression. These problems are reflected in medication non-adherence and self-care behavior neglect [36–38], which results in poor glycemic control and high glucose levels.

Diabetes and stress are both causes and effects of one another. This is due to the fact that stress raises blood sugar and HbA1c levels; yet, the management and treatment of the illness itself can result in high levels of stress [36].

According to certain research, specific tactics including stress reduction methods [36–38], mindfulness practices [38], and other cognitive–behavioral therapies [37] can reduce depression, general stress, anxiety, and diabetes-related distress. The improvement in patient well-being is reflected in improved self-care and commitment to their treatment, which also helps to prevent long-term complications [36]. Therefore, further research is required to completely comprehend how treatments for high stress, depression and anxiety might impact glycemic control [36–38].

2.2 Technical background

In this work, two different approaches are established to create the prediction and recommendation modules. Data-driven models were used to create the prediction model for glucose forecast based on the past glucose levels of patients. Knowledge-driven models were used for the recommendation module to infer useful recommendations from collected data and offer it to the user in a personalized way.

2.2.1 Data-driven models

As noted earlier, diabetes self-management relies on the blood glucose prediction as it allows taking suitable actions to prevent hyperglycemic/hypoglycemic episodes. Due to the fact that such measurements follow a chronological order, we treat the challenge of estimating future blood glucose levels as a time series forecasting problem. Time series prediction aims to collect previous data, prepare it for algorithms to use, and then predict future values based on patterns discovered from the current and previous data. This problem may be generalized by Equation 2.1.

$$\hat{x}_{t+PH} = f(x_t, x_{t-1}, x_{t-2}, ..., x_{t-N+1}) \tag{2.1}$$

For an observed time series x with N points, t represents the glucose value at the current time t. PH is the prediction horizon, i.e. the number of time steps from the current point to the prediction point. Therefore, through a function f it

is possible to estimate a future value at $t + PH$. This function is a model that can be used to get an estimated value to $\hat{x}_{t+PH}$.

Since only glucose values recorded through a Continuous Monitoring Device (CGM) will be used as input to the prediction algorithm, it is an univariate time series problem. The time series prediction can be framed as a supervised learning problem. The machine learning task of supervised learning is to train a function that translates input to an output using examples of input-output pairs. Each example in supervised learning is a pair that includes an input item and the desired output value. An inferred function is generated by a supervised learning algorithm from the training data, which may then be used to map new samples. The algorithm will be able to accurately determine the class labels for instances that are not yet visible in an ideal environment.

Turning a time series dataset into a supervised learning problem can be done by framing the data using the sliding window method. This re-framing of the time series data allows access to the set of standard linear and non-linear data-driven models on the problem. The figure 2.2 schematizes a general description of how the data are framed to be used by the models. The input data is splited as long as the lookback period (which indicates how many previous values should be used simultaneously by the algorithm) and the set of times within the lookback is considered as a sample. A sliding window with a step size of one generates each sample. The Prediction Horizon (PH) or delay specifies the target value that the algorithm should predict. Thus, a pair input-output is composed of a set of previous values within the lookback period and a target value.

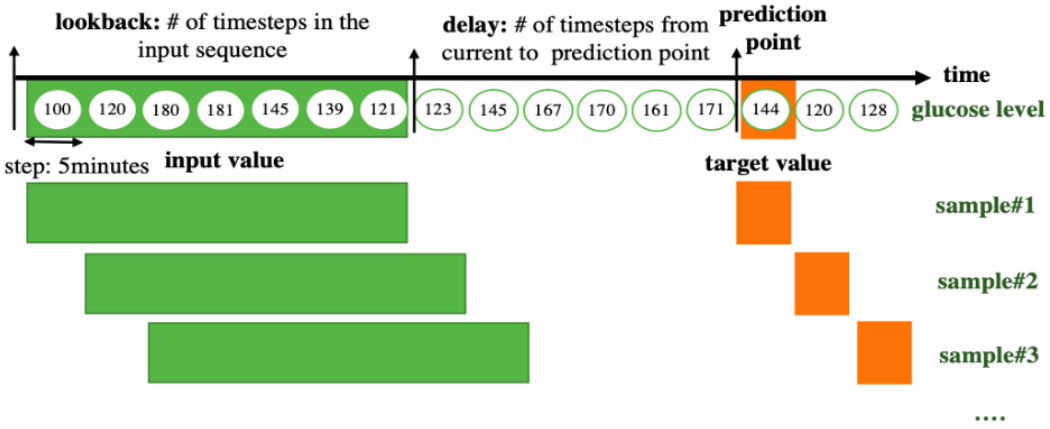


Figure 2.2: Overall description of how the data are framed to be fitted to the data-driven models and become a supervised learning problem. From [39].

So, data from each subject is transformed into pairs (x_n,y_n), where the vector

x_n is a CGM time series segment of length equal to the size of lookback, i.e., from $n-L+1$, where L corresponds to the lookback, to n which corresponds to the final moment of the sequence of values to be used as input, $x_n = [x_{n-L+1}, ..., x_{n-1}, x_n]$ and y_n is CGM time-series value at the time $n+PH$ with respect to the prediction horizon PH given in samples, $y_n = x_{n+PH}$.

Numerous investigations have been made to develop models to predict the blood sugar level in order to give the subject advanced warning. In the next chapter, in Section 3.2, the most successful models in the literature for predicting future glucose values will be presented (Autoregressive Integrated Moving Average (ARIMA), Case-based reasoning (CBR), Recurrent Neural Network (RNN), Long Short-Term Memory (LSTM), Gated Recurrent Unit (GRU) and Jump Neural Network (JNN)). For a better understanding of these, the next section will explain the key concepts and how these data-driven models are used to forecast future values.

2.2.1.1 Autoregressive Integrated Moving Average

ARIMA models are considered some of the most flexible and popular autoregressive techniques for continuous time series forecasting [40]. This models generally use the historical values of a univariate time series to predict future time series values. In a ARIMA model, the future value of a variable is assumed to be a linear function of several previous observations and random errors [41]. AR stands for "autoregressive", and is a stochastic process whose output values are linearly dependent on the weighted sum of their prior values and a white noise error [41]. Integrated means that the variance has been removed (if present) for differentiating the time series [42]. MA stands for "moving average", and describes a stochastic process whose output value is linearly dependent on the weighted sum of a white noise error and the error term from previous periods [41]. One of the tasks for constructing the ARIMA model is to determine the value of (p, d, q) [41]:

p: order of the autoregressive part (AR);

d: degree of first differencing involved;

q: order of the moving average part (MA).

The least-squares or maximum likelihood estimation methods are typically used to estimate the parameters of ARIMA models [41].

When working with a data sequence $x_1, x_2, ..., x_t$ we can describe ARIMA as [40, 41]:

$$x_t^{'} = c + \phi_1 x_{t-1}^{'} + ... + \phi_p x_{t-p}^{'} + \epsilon_t + \theta_1 \epsilon_{t-1} + \theta_q \epsilon_{t-q} \tag{2.2}$$

where $x_t^{'}$ denotes the differenced time-series, which has been differenced d times,

c is a constant, ϕ is the AR(p) coefficient, θ is the MA(q) coefficient, and ϵ is the lagged forecast errors.

2.2.1.2 Case-Based Reasoning

CBR is a methodology based on the intuition that similar problems often have similar solutions [43]. It is described as a paradigm of thinking that combines memory processes with problem solving, knowledge, and learning. It entails modifying earlier answers to satisfy new requirements, referencing earlier situations to explain or defend new solutions, and drawing inferences from the past to interpret the present [44]. CBR provides an inherent model-specific approach to interpretability [43].

A *case* is represented as the ordered pair *(problem, solution)* [43]. As mentioned earlier, in this project the CGM data is organized as pairs (x_n, y_n). In this context, x_n corresponds to the *problem* and y_n to the *solution*. Thus, a *case base* is created with all *cases* from all training patients. Different global distance functions can be used to find similar *cases* in the *case base* for each new query case such as Minkowski distance, Cosine distance, Euclidean distance, City Block distance, Pearson's correlation coefficient distance, etc. This model reuses remembered experiences, where the experience need not record how the solution was reached, simply that the solution was used for the problem [45]. The *solution* is learned from the set of existing instances in the *case base* for each new instance of the problem [44].

In the context of prediction, the model is provided with a new instance, i.e., a segment of CGM data, in order to predict a certain value in the future. This input (the *problem*) will be compared with other *cases* present in the *case base*. This is adapted for the forecasting horizon in question. This means that for a forecast in a specific time horizon there must be a *case base* in which the pairs (*problem, solution*) are also for that prediction horizon. The forecast is achieved by adopting the value of the *case solution* that gets the smallest value assigned by the chosen distance function.

The intuitive appeal of CBR comes from its similarity to human problem-solving behavior. CBR can be based on surface-level knowledge and does not necessitate as much knowledge engineering work as other Artificial Intelligence (AI) fields like rule-based reasoning do. This is similar to how people use prior experience to solve new problems, which frequently does not require in-depth analysis of the problem domain [44].

There are several proposed models of CBR and the most used model is the R4 model [44]. The process involved in this model can be represented by a schematic

cycle composed of the four R's, as illustrated in Figure 2.3.

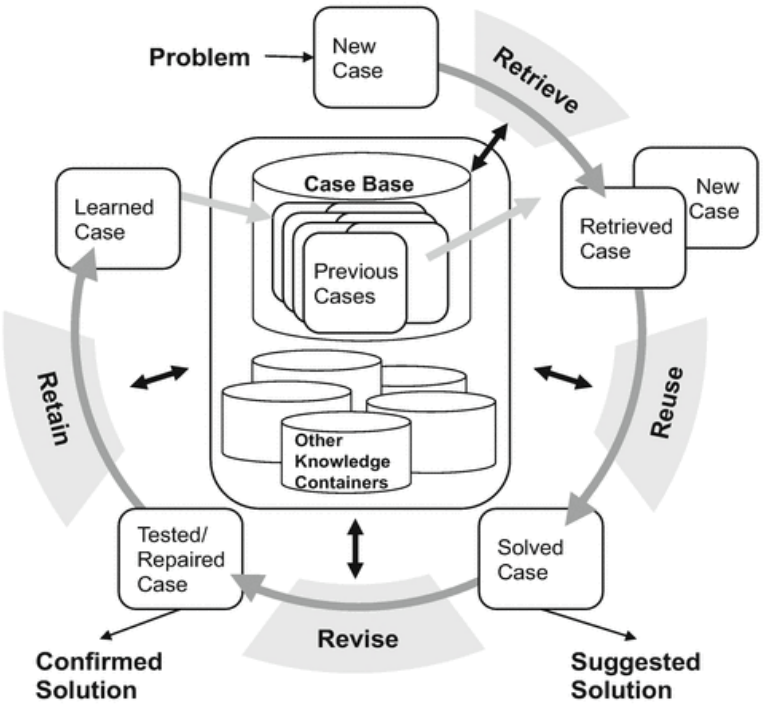


Figure 2.3: The R4 Cycle. From [45].

2.2.1.3 Artificial Neural Network

Artificial Neural Networks (ANNs) are a machine-learning method that imitates the biological function of the human cerebral cortex. These are among the most widely used techniques in medicine and many other areas and have excellent effectiveness with both linear and non-linear data [46]. By linking layers of neurons, as the name implies, they attempt to mimic the behavior of the brain's network of neurons, with each neuron having a unique weight, polarization, and activation function. The activation function translates the inputs' non-linear relationships into a more usable output. ANNs are a great tool for the prediction task due to the many associated advantages: robustness due to the use of weights even in noisy environments, low error rate, high degree of accuracy and performance improvement with the ability to learn in the training phase [46].

Due to its effectiveness solving nonlinear issues, Feed-Forward Neural Networks (FFNNs), also known as multilayer perceptrons, are the most used type of ANN. Such neural networks typically consist of an input layer, at least one layer of neurons that are hidden, and an output layer. The first hidden layer receives the initial data transmission from the input layer. Every neuron in this sends signals to the

neurons in the second hidden layer (again, modulated by weights). The data is transformed as it passes through each hidden layer in an effort to identify, if possible, the discriminative behavior that exists there. A certain classification is produced upon reaching the output layer.

This network has the general structure shown in Figure 2.4 and is expressed as Equation 2.4.

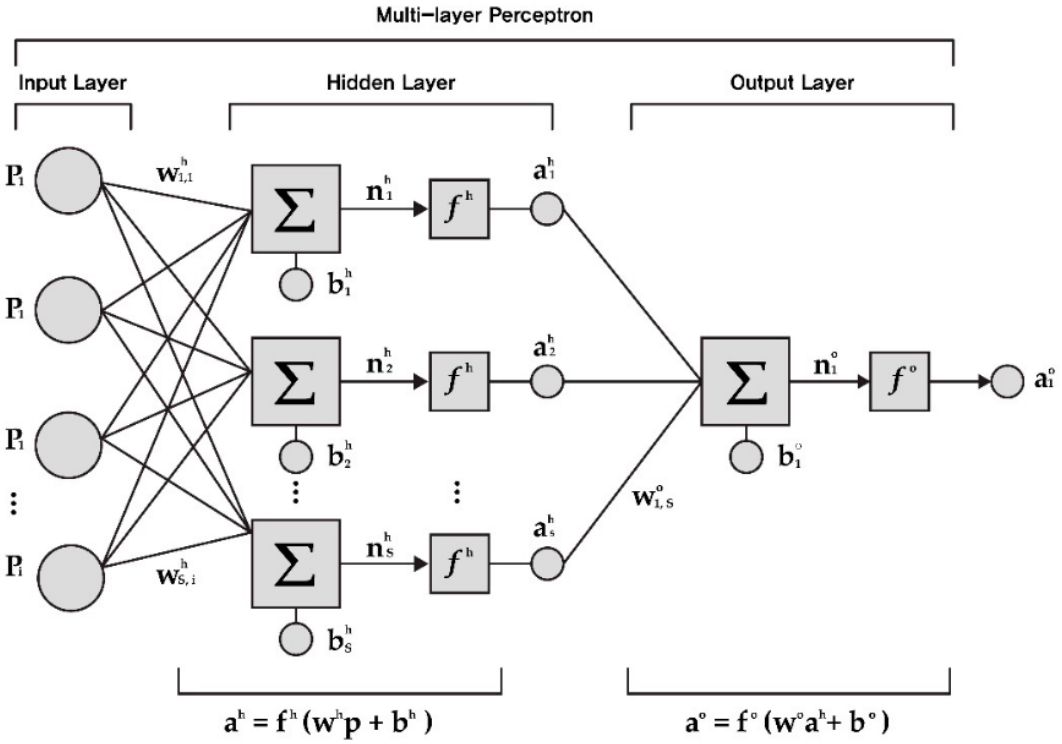


Figure 2.4: Structure of FFNN model. From [47].

$$n_k^h = \sum_{j=1}^{R} w_{k_j}^h p_j + b_{h'}^k, k = 1 \; to \; S \tag{2.3}$$

where R is the number of input variables and S is the number of hidden neurons. Further, p is the input variable, b^h is the bias of the hidden layer, and w^h is the weight. The calculated value is used as input for an activation function. The input of the FFNN is processed to obtain the output by modifying the weight sum of the values from the previous layer by using the activation function [47]. In this prediction problem, the input variable corresponds to the past glucose values.

2.2.1.4 Jump Neural Network

JNNs consists of a FFNN with the addition of direct connections from each input to the output neuron [48]. This means that the inputs are connected not only to the first hidden layer but also to the output layer [49]. Such a framework is especially well suited for time series fitting and forecasting that include both linear and non-linear dynamics found in the physiological data [48]. Hidden neurons, with their non-linear activation functions, model the non-linear relationship between inputs and targets, while output neurons, with their linear activation functions, learn the linear relationship between inputs and targets [49]. The architecture of these Neural Network (NN) is schematized in Figure 2.5.

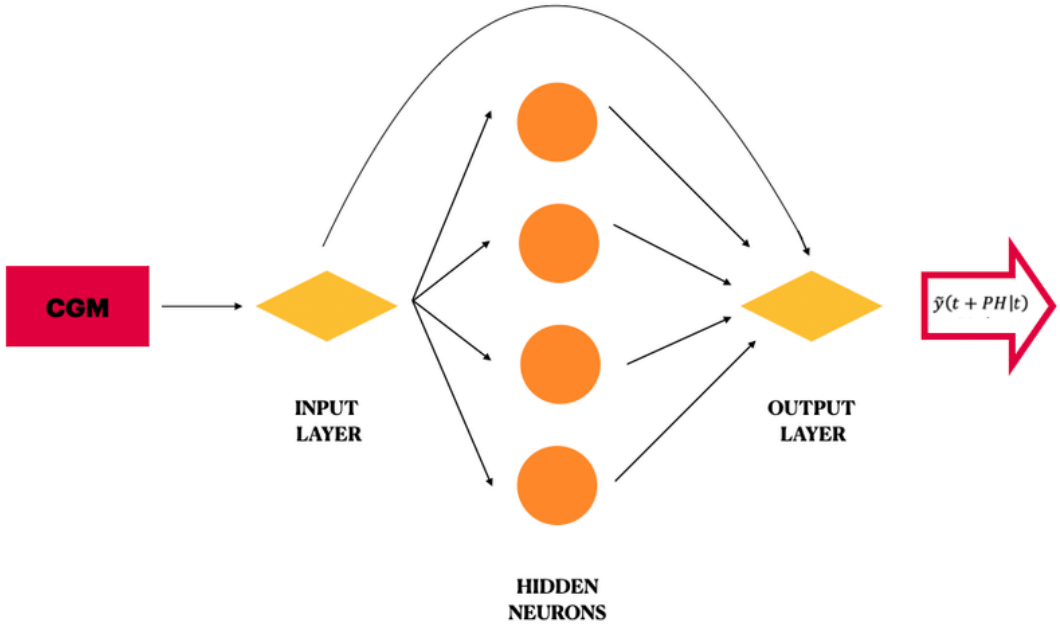


Figure 2.5: Schematic illustration of JNN. The input is directly connected to the hidden neurons and to the output layer. Where $\tilde{y}(t+PH|t)$ corresponds to $\hat{x}_{t+PH}$. From [50]

At each timestamp t, the Jump Neural Network predicts a signal that can be expressed as [50]:

$$\hat{x}_{t+PH} = O \cdot I(t)^T + V \cdot f(P \cdot I(t)^T) \tag{2.4}$$

where $I(t)$ is a row vector with L elements corresponding to the $x[t-L+1, t]$, O is a row vector with L weight elements directly connecting every input to the output neuron, V is a row vector of H weights connecting every hidden neuron to the output neuron, P is a $H \times L$ matrix of weights connecting every input to every

hidden neuron and f is the tangent-sigmoid activation function, computed element-wise on the results of $P \cdot I(t)^T$. The first term models the linear relationship between the target and the inputs, whereas the second term models the nonlinear relationship [50].

2.2.1.5 Recurrent Neural Network

A RNN is an extremely powerful model that can classify, cluster, and make predictions about data, particularly time series [51]. By maintaining an internal memory that enables them to develop sequential rules, RNNs use data from the past or the future to learn about the current data. However, if the sequences are quite long, the gradients (which are crucial for adjusting the weight and bias) are computed during their training (backpropagation). They either vanish (multiplication of numerous small values less than 1) or explode (multiplication of many large values greater than 1), causing the model to train very slowly [51]. As a result, many RNN types have been created to address these issues.

LSTM is a modified RNN architecture that solves the aforementioned problems. In LSTM, the leak or burst gradient problem is resolved by using a series of gates to regulate when data enters memory [51]. Recurring connections provide the network with additional state or memory, enabling it to learn and benefit from the ordered pattern of observations in input sequences. Network outputs are dependent on recent context in the input stream rather than what was just supplied as input to the network due to internal memory [51].

The GRU is a type of RNN structure with fewer gates compared to LSTM. One gate controls both the input and forget gates in the GRU cell unit. The GRU is therefore simpler than the LSTM since the forget gate and input gate are integrated into one gate.

Data from one time step has relevance over data from earlier time stages in a sequential or temporal input. The forecast at any given time depends not just on the current input but also on the prior experience. In other words, another dimension, namely temporal ordering, is also taken care of in all RNN model calculations. This philosophy is the backbone of the RNN computation [52]. The model is usually trained using the backpropagation through time algorithm that incorporates the notion of the time/sequence in the underlying gradient descent process [52].

The unit cells of each type of RNN are illustrated in figure 2.6. For each architecture, the equations necessary for their better understanding have been explained. In the equations corresponding to the RNN, i.e. Equations 2.6 and 2.7, U, V, and W are the shared weight matrices from input-to-hidden, hidden-to-output, and be-

tween consecutive hidden nodes respectively at all time steps. b_s and b_o are the biases for the hidden node and the output node, respectively. For the equations corresponding to the LSTM and GRU, i.e., Equations 2.8 - 2.17, subscripts of the weight matrices and biases indicate the initial of the gate.

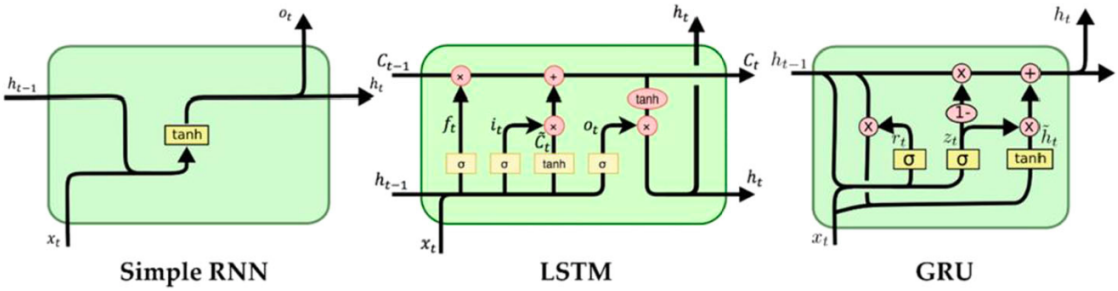


Figure 2.6: The indepenent cells of RNN, LSTM and GRU. From [52].

The sigmoid and tanget activation functions are represented by the following equations:

$$tanh(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}} \qquad sigmoid(x) = \frac{1}{1 + e^{-x}} \tag{2.5}$$

The structure of the simple RNN cell consist of hidden state (h_t) and output (o_t) - Equations 2.6 and 2.7.

$$h_t = tanh(W \times h_{t-1} + U \times x_t + b_s) \tag{2.6}$$

$$o_t = \sigma(V \times h_t + b_o) \tag{2.7}$$

The information flow in the network is controlled by the internal gates of LSTM and GRU cells. Important information is stored and transferred further in every cell function, while unnecessary information is suppressed. During the model's training phase, the network learns which information is important and should be retained or ignored. This is achieved by storing cell-state information that functions as a conveyer belt, adding the essential information as needed and removing the unneeded information. Here, sigmoid activation plays a crucial role in separating the relevant information from the irrelevant data, as this function squishes between 0 and 1 [52].

The structure of the LSTM cell consists of hidden state (h_t) and four gates, i.e., input gate i_t, forget gate f_t, control gate C_t, and output gate o_t. From Equation 2.8 to Equation 2.13 the gates mentioned are explained [53].

The input gate determines what data may be sent to the cell - Equation 2.8.

$$i_t = \sigma(W_i \times [h_{t-1}, x_t] + b_i) \tag{2.8}$$

The forgot gate decides which information from input should be neglected from the previous memory - Equation 2.9.

$$f_t = \sigma(W_f \times [h_{t-1}, x_t] + b_f) \tag{2.9}$$

The control gate controls the update of cell state from C_{t-1} to C_t - Equations 2.10 and 2.11.

$$\tilde{C}_t = tanh(W_c \times [h_{t-1}, x_t] + b_c) \tag{2.10}$$

$$C_t = f_t \times C_{t-1} + i_t \times \tilde{C}_t \tag{2.11}$$

The output gate is responsible for generating the output and updating the hidden vector h_{t-1} - Equations 2.12 and 2.13.

$$o_t = \sigma(W_o \times [h_{t-1}, x_t] + b_o) \tag{2.12}$$

$$h_t = C_t \times tanh(o_t) \tag{2.13}$$

Moreover, the cell equations for GRU consist of reset gate (r_t), update gate (z_t) and hidden state (h_t). The gates mentioned are described from Equation 2.14 to Equation 2.17.

The reset gate determines how to combine the new input with the previous memory to calculate the new state - Equation 2.14.

$$r_t = \sigma(W_r \times [h_{t-1}, x_t] + b_r) \tag{2.14}$$

The update gate is responsible for the collective functioning of the forget and input gate of a LSTM cell - Equation 2.15.

$$z_t = \sigma(W_z \times [h_{t-1}, x_t] + b_z) \tag{2.15}$$

$$\tilde{h}_t = tanh(r_t \times [h_{t-1}, x_t] + b_h) \tag{2.16}$$

$$h_t = z_t \times \tilde{h}_t + (1 - z_T) \times h_{t-1} \tag{2.17}$$

In Table 2.1, a comparison of these three RNNs in terms of model complexity, key characteristics, and shortcomings are presented.

Table 2.1: Comparative analysis of RNN and its architectural variants [52].

	Simple RNN	**LSTM**	**GRU**
Model complexity	Low	High	Moderate
Key characteristics	Easier to train Less computational resources	Model long term dependency Extraction of contextual information	Model long term dependency Extraction of contextual information
Shortcomings	Vanishing gradient problem	High hidden layer complexity	Higher complexity than simple RNN

2.2.2 Knowledge-driven models

Recommendation systems (RSs) consist of technologies that are efficient at extracting valuable information and then using it effectively [54]. These are generally motivated by the need to support user decision-making and provide an automated, online, and generally personalized filtering mechanism that enables users to cope with information overload [55]. The technical specifications and appropriate design based on the system's kinds and functions determine how capable these systems are. There are four general categories of RSs: Collaborative Filtering (CF), Content-Based (CB), Knowledge-Based (KB), and Hybrid Recommender systems (HRS) [54, 55].

Systematic utilization of relevant and timely data, information, and knowledge management is the goal of KB decision support systems, which are intended to enable more accurate decision-making. These systems refer to decision-making based on relevant knowledge, which relies on AI, and the application of information and communication technologies [56]. These systems also provide decision-making assistance using prediction and recommendation methods [56]. Three different categories of knowledge must be used by Knowledge-Based Recommendation Systems (KBRSs): knowledge about the users, knowledge about the items, and knowledge about the compatibility of the item with the user's needs [57].

While all intelligent recommenders implement knowledge of some kind, KBRSs focus on domain knowledge and constraints, or in other words, the knowledge that is not yet exploited in content-based or collaborative techniques [55]. Since suggestions are created without taking into account the user's history and simply taking into account the needs of the recommender session, KBRSs have one benefit over the other two basic recommender techniques in that cold-start issues are avoided.

However, KBRSs suffer from a difficulty of their own in the form of the knowledge-acquisition bottleneck: requiring the transformation of domain expertise into formal representations [55].

A way of implementing KBRS is using Rule-based systems (RBSs) - also known as production or expert systems - which are the simplest form of artificial intelligence [58]. A rule-based system uses predetermined rules to organize, store, and process data. It imitates human intelligence in doing so. A rule-based system is a way of encoding the knowledge of a human expert in a just and narrow area into an automated system. This knowledge can be acquired in many ways, in the context of diabetes, guidelines from studies and authoritative public documents from internationally recognised associations can be analysed and guidance can be sought from a health professional in the field to cover details that are not specified in the guidelines.

A collection of assertions and a set of rules that describe how to respond to the set of assertions may easily be combined to build a RBS [58]. The rules are expressed as a set of if-then statements (called IF-THEN rules or production rules) [58]:

IF P THEN Q, which is also equivalent to $\mathbf{P} \Rightarrow \mathbf{Q}$

According to the aforementioned formula, the output (effect, consequent, result) may be deduced if the input (cause, antecedent, condition) is provided [59]. This type of system consists of a set of IF-THEN rules, a set of facts, and some interpreter who controls the application of the rules, given the facts. The expert system should behave similarly to the expert when presented with the same data. RBSs are incredibly flexible models that may be used to solve a variety of problems. The requirement is that knowledge about the problem area can be expressed in the form of IF-THEN rules. The area should also not be so large because a large number of rules can make the problem solver (the expert system) inefficient [58].

Any RBS consists of a few basic and simple elements, as follows [58]:

1. **A set of facts.** These assertions are facts and must contain information about the system's starting condition.
2. **A set of rules**. This enumerates all the necessary steps to be followed in the event of a problem and details how to respond to the collection of assertions. A rule relates the facts in the IF part to some action in the THEN part. The system should contain only relevant rules and avoid irrelevant ones because the number of rules in the system will affect its performance.
3. **A termination criterion.** That's the circumstance that establishes whether

a solution has been found or whether there is none. This is required to stop some rule-based systems from looping indefinitely.

3

State of the art

This chapter reviews the state of the art related to the two modules of this thesis. Section 3.1 starts by presenting some approaches regarding telemonitoring and self-management of type 2 diabetes. Next, in Section 3.2, we present the most successful data-driven models in the literature for the prediction of future glucose values. In Section 3.3, we also present the international guidelines with some of the consensus reached by scientists and health professionals mainly on diet and exercise, as well as some examples of recommendation systems in this context. The chapter ends with some pertinent conclusions in Section 3.4.

3.1 Telemonitoring and self-management of T2DM

In patients with Type 2 Diabetes Mellitus (T2DM), it is important to have sufficient knowledge about the disease. Empowering the patients, which means increasing their ability to determine their decisions and self-care activities for their health, is amplified with the use of diabetes technologies [2]. Several studies have shown that using these methods can reduce the level of Hemoglobin A1c (HbA1c), endorse behavioral changes, improve psychological status, and increase health literacy, self-care and control [2].

Changes in patients' lifestyles, including weight loss, increased physical activity and adoption of a healthy diet, are one of the first-line strategies for the management of T2DM [60]. Devices that allow continuous monitoring of glucose values and smartphone applications that help and encourage these changes allow for greater proximity to the disease and consequently improve glycemic control, preventing dangerous episodes for the health of patients.

3.1.1 Blood glucose monitoring

Several enzyme-based electrochemical glucose sensors have been developed for blood glucose monitorization. These sensors use glucose oxidase (GO_x), which oxi-

dizes glucose and produces gluconic acid and hydrogen peroxide (H_2O_2) – Equation 3.1.

$$Glucose + H_2O \xrightarrow{GO_x} Gluconic\ acid + H_2O_2 \tag{3.1}$$

The sensors monitor the fluctuations in O_2 or H_2O_2 concentration, which generate a small electrical current, that is measured by electrodes and transformed through calibration to display the glucose concentration value [61]. Even though a few alternative methods for glucose level measuring have been developed, such as electrocatalytic mediators and structurally modified enzymes, this method of electrochemical byproduct detection remains the standard for glucose monitoring, although it has the limitation of requiring the consumption of O2 in order to work. This problem was resolved through the use of semipermeable membranes capable of supplying the necessary O_2, but the development of a oxygen free efficient glucose detection sensor would still be preferable.

In order to perform Self-Monitoring of Blood Glucose (SMBG), tape-type glucometers are still the most widely employed solution, although their use is being replaced by technologies incorporating microneedles. Tape-type glucometers consist of portable glucometers that have connected to them a disposable strip with a multilayer capillary channel, that collects blood and analyzes it, displaying the glucose concentration in the plasma [62]. These systems are widely used due to the low cost, simple, easy and immediate nature of the measurement, but since it usually is performed only 3-4 times a day, its' sampling frequency makes it unable of providing a fully continuous profile of glucose levels, neglecting hypoglycemia or hyperglycemia episodes that might happen between measurements.

Blood glucose monitoring has been revolutionized in the last few decades by Continuous Monitoring Device (CGM) sensors, which are temporary minimally invasive sensors inserted in subcutaneous tissue with a glucose-oxidase doped platinum electrode deposited on its needle [63]. These sensors can deliver an almost continuous glucose trace, providing more complete and clinically relevant information than SMBG systems. In the last decade, manufacturers have focused on increasing the comfort levels of the patient, the features available and the accuracy of their devices, measured by Mean Absolute Relative Difference (MARD) – Equation 3.2.

$$MARD = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{BG_i - Comp_i}{Comp_i}\right| \tag{3.2}$$

in which BG_i is the i-th Blood Glucose (BG) or CGM result and $Comp_i$ is the corresponding comparison method's result. Lower MARD values indicate a

better analytical performance [64]. CGM sensors in the market already achieve a 9% MARD [65].

The uptake of CGM sensors has been rising slowly. Most reservations regarding these systems are related to the high costs, with a traditional CGM sensor costing 3000$ to 5000$ per year [66], lack of insurance coverage, the dislike of having to wear a device on your body, and the perceived low accuracy. These barriers, however, have started to be lifted in the last few years, with manufacturers building better, more comfortable, and less expensive devices, reaching 900$ to 1800$ per year, with some studies claiming potential 685$ to 950$ savings per year in total healthcare costs when using CGM systems [66].

Even though the beneficial effects of CGM have been more intensively studied in Type 1 Diabetes Mellitus (T1DM) and T2DM patients on intensive insulin treatments, the Endocrine Society recommends intermittent use of personal CGM devices for willing T2DM patients with poor glycemic control [65]. This device carries several benefits such as greater HbA1c reductions when compared with SMBG with standard education [67], and higher success in the prediction of hyperglycemic/hypoglycemic episodes as it continuously captures information that allows knowledge of important metrics such as time in range, time in hypoglycemia, glucose variability, and others [68]. One other advantage of CGM devices is the biofeedback they can provide in real-time. Being able to continuously watch real-time data on a connected device, including visible trends and trajectories, help patients understand and learn about their bodies and glycemic responses (seeing, for example, which foods and exercises affect them the most), which is very important since diet, physical activity and behavioral therapy are the cornerstones of T2DM management. Studies suggest that short-term use of real-time CGM (RT-CGM) that incorporates graph interpretation and hyperglycemic alarms without counseling can increase physical activity levels and adherence to a physical activity routine, as well as reductions in food portions and caloric intake [69].

In development are also noninvasive and patient-friendly monitoring systems of BG. With physical pain, discomfort and inconvenience still constituting a limitation even in minimally invasive devices, a few alternatives have been studied using different biofluids, such as contact-lenses sensors using tears, mouthguards sensors that use saliva, microneedles using interstitial fluid, and wearable wristbands that use sweat, just to name a few [12]. Once more studies are made and these products are commercialized, CGM adhesion by T2DM is predicted to rise.

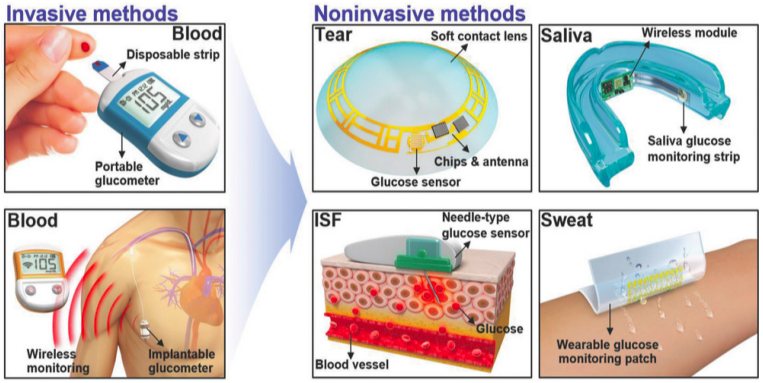


Figure 3.1: Invasive and non-invasive electrochemical glucose monitoring systems. In the figure, on the invasive methods side, the upper method depicts tape-type glucometers and the lower one the CGM device. From [12].

3.1.2 Mobile applications

With the evolution of mobile technology, there are currently a large number of applications aimed at increasing patient self-management skills, facilitating communication between the patient and healthcare providers and also increasing patient adherence to treatment [70].

Veazie et al. [71] analyzed six studies evaluating five commercially mobile applications for T2DM (BlueStar Diabetes, WellTang, NextJ Connected Wellness Platform Health Coach +, Gather Health, and mDiab). In general, apps track BG, exercise, HbA1c, prescriptions/medication, and weight providing feedback like medication reminders, BG level alerts, BG measurement reminders, diabetes education, and HbA1c calculation. The authors concluded that despite some limitations, there is evidence that the use of apps with the additional support of a healthcare professional can be useful, especially in improving the HbA1c value, compared with controls in randomized controlled trials. Even with a stricter criterion for clinical improvement in HbA1c (reduction of 0.5% or more), 3 of the apps were associated with improvements. However, the evidence does not indicate that using apps improves other important outcomes, such as quality of life, blood pressure, weight, or Body Mass Index (BMI).

Bellei et al. [7] analyzed 39 studies on mHealth in diabetes to perform a systematic review of features and fundamentals. The selected articles were published between 2009 and 2017. All technologies present in the studies fall into the mHealth category, and 11 studies also have a web page where patients and health professionals have access to treatment information. The authors aimed to map a panorama of solutions presented in the literature and those available to the public at the same time. In this research process, they found that few initiatives aim to make solutions

developed in scientific research available to end-users. Among the inclusion criteria selected by the authors, the following commercial applications were found: Bant, myFitness Companion, Diabetes Notepad, TreC Lab, Diabetes 101, and IDM. All apps had at least two features. 89.7% (35 apps) have a record of all essential tasks for the treatment of Diabetes Mellitus (DM), such as blood glucose, food intake, medication, and physical activity. The remaining apps focus only on diet or exercise. All mobile applications have the manual input of glucose values, 12 of which allowing connection with electronic devices to automate data collection. In addition to operating as logbooks, 11 of these apps perform tasks such as counting carbohydrates ingested or calculating insulin dosage. Nearly 50% of applications (18) use the recorded data to create personalized recommendations for patients. Most applications are based on guidelines and recommendations from healthcare organizations, perform clinical trials, and use evaluations from health professionals and patients to validate the technology. However, some limitations were pointed out in the study. The functionalities of some applications did not adequately address the handling tasks, partially recording the data or not displaying reports on the recorded data. Some failures were pointed out in the mention of important comorbidities in this pathology such as foot care and sensitivity of body members to prevent peripheral neuropathy and issues such as water intake, urinary frequency, and association with glycemic control to prevent nephropathy. In addition, the specific use of typical drugs for T2DM, such as metformin and sulfonylureas, was not addressed in any of the apps.

To verify how effective these apps are and what impact they have on patient education and behavioral interventions, Wu et al. [15] performed a meta-analysis of randomized controlled trials comparing smartphone technologies with usual diabetes care among T2DM patients. 17 studies (2225 participants) were included from Asia, North America, Europe and Africa, conducted between 2008 and 2016. mHealth interventions significantly reduced HbA1c (pooled weighted mean difference of 0.51%). For patients with this pathology for less than 8.5 years, this improvement was even higher, reaching a pooled weighted mean difference of 0.83%. The rest of the patientes had an average difference of 0.22%. Regarding the control groups, the authors concluded that patients who used mHealth improved glycemic control, especially those who are in the early stages of the disease (diagnosis duration <8.5 years), thus being, these technologies can be an adjunct or alternative to patient education and behavioral interventions. It was further mentioned that no subgroup differences were found between different durations of follow-up, study sites, age of patients, length of contract with the healthcare professional, baseline

BMI and baseline HbA1c.

3.2 Glucose level prediction

In the last decades, due to the development of more powerful and accurate data logging devices and more sophisticated machine learning models, glucose prediction in the context of diabetes has been studied by researchers in many disciplines [72, 73]. Numerous approaches to predict glucose levels, based on physical models or data-driven empirical models, were developed [43, 72].

These models estimate future blood glucose levels over various prediction horizons in an effort to identify and stop harmful outcomes [48]. Most models focus only on T1DM, while literature regarding predictions in T2DM is scarce [48]. This is mainly due to the fact that the goal of modern science in diabetes therapy is to develop a closed-loop system to control blood glucose ("artificial pancreas") [74]. Accurate short-term predictions (with a prediction horizon of 30 to 60 min) are the basis for the implementation of the artificial pancreas that makes the life for T1DM patients easier and more convenient [75].

Numerous methods for short-term glucose prediction have been presented in the literature since the development of CGM, and these may be roughly divided into two groups: i) approaches based on a priori physiological models, which aim to replicate a patient's metabolic response using equations that quantitatively characterize glucose kinetics; ii) data-driven approaches, which extrapolate future glucose concentration levels using models trained on real glucose data [73]. Since our study belongs to the second category, we only focus on the recent developments in data-driven models.

As mentioned before, in the literature, various approaches have been proposed to predict blood glucose levels. Sparacino et al. [76] compared the predictive performance of a first-order polynomial model with a first-order Autoregressive (AR) model, both with time-varying parameters determined by weighted least squares. Using 28 participants with T1DM, they collected glucose for 48 hours while monitoring it every three minutes using a CGM device. For Prediction Horizons (PHs) of 30 and 45 minutes, the Root Mean Square Error (RMSE) values are 18.78 and 34.64 mg/dL. They demonstrated that glucose may be forecasted in advance even utilizing this straightforward approach.

Regarding machine learning techniques used for estimate upcoming values of BG levels, Pérez-Gandia et al. [77] used a Feed-Forward Neural Network (FFNN) composed of 3 layers. Data were collected from 15 patients with CGM devices, and sampling frequencies ranged from 5 to 15 min. The inputs of the Artificial Neural

Network (ANN) were the values provided by the CGM sensor during the preceding 20 min, while the output was the prediction of glucose concentration at the chosen PH time. The results were evaluated as an RMSE of the difference between the predicted blood value and the unused data during the ANN training set. The RMSE were 9.7 mg/dL, 17.5 mg/dL, and 27.1 mg/dL for PHs 15, 30, and 45 min, respectively. A few years go by, Ali et al. [78] proposed an improved method based on ANN using only CGM data as inputs, validated on real CGM data of 13 patients. The obtained averages of RMSE were 6.43 mg/dL, 7.45 mg/dL, 8.13 mg/dL and 9.03 mg/dL for PHs respectively 15 min, 30 min, 45 min and 60 min. An strategy to forecast blood glucose levels for diabetic patients using deep learning techniques was reported in the research work in Martinsson et al [79]. The authors used the Ohio T1DM Dataset for Blood Glucose Level Prediction to validate an Long Short-Term Memory (LSTM) model. They obtained RMSE values of 18.87 mg/dL for a 30 min prediction horizon and 31.40 mg/dL for a 60 min prediction horizon. This study pointed out that larger data sets and standards are needed. A patient-specific prediction model based on LSTM was also trained and validated using the OhioT1DM dataset by Aliberti et al. [80]. The patient with the best predicted outcome out of the six patients had RMSE values of 11.55 mg/dL, 19.86 mg/dL, 25 mg/dL, and 30.95 mg/dL for 30, 45, 60, and 90 min. A similar study can be found in Sun et al. [53]. The authors used an LSTM model and an Bidirectional Long Short-Term Memory (BiLSTM) based on the BG signal to predict upcoming values for BG levels and compared results with Autoregressive Integrated Moving Average (ARIMA) and Support Vector Regression (SVR) models. The LSTM results outperformed the previous methods, achieving RMSE values of 11.6 mg/dL, 21.7 mg/dL, 30.2 mg/dL and 36.9 mg/dL for prediction horizons of 15, 30, 45 and 60 min, respectively.

In 2012, Zecchin et al. [81] proposed a predictor that combines a Neural Network (NN) model and a first-order polynomial extrapolation algorithm used in parallel to describe, respectively, the nonlinear and linear components of glucose dynamics. This model exploited the CGM data and ingested carbohydrate information for a 30 min PH. To assess the solution, 9 daily profiles were used and the average results of RMSE were 14 mg/dL. The research demonstrated that incorporating information about carbohydrate consumption increases the precision of short-term predictions of glucose concentration. Then the same authors did another study [49] where they simplified the structure of the network and called it a Jump Neural Network (JNN). The NN was tuned on data from 10 T1DM and then evaluated in 10 different subjects. In this time, the average results of RMSE were 16.6 mg/dL, for the same PH. Although the second study had a simpler network, the two studies showed no

statistically different differences.

Regarding the prediction of glucose values for patients with type 2 diabetes, one study was found for hospitalized patients with this disease. Kim et al. [39] collected data from 20 patients for one week on a CGM device. The model used the last 35 minutes to predict blood sugar for the next 30 minutes. Three prediction models were compared, simple Recurrent Neural Network (RNN), LSTM and Gated Recurrent Unit (GRU) where the latter showed the best performance. As a result, a RMSE of 21.5 mg/dL and a Mean Absolute Percentage Error (MAPE) of 11.1% were obtained. The writers concluded that it is possible to forecast the blood glucose level of these patients due to the low prediction error of the proposed method. They stated that the model may be improved by assessing patient variables besides blood glucose and by increasing the test database.

Table 3.1 summarizes the performance and information of the models mentioned above.

Thus, it becomes evident that deep learning based black-box models constitute the majority of the state of the art in glucose prediction. However, these approaches carry significant limitations in interpretability, which becomes critical in algorithms that directly affect patient care. In order to overcome this difficulty, Zulj et al. [43] implemented case-based reasoning for glucose prediction using CGM data. This approach, which was based on the idea that the solution to a new problem can be given by adapting solutions from similar known cases, allowing greater interpretability of the model to be achieved. The study was conducted using data from 20 subjects recorded under free-living conditions. The best models developed by the authors achieved a Mean Absolute Error (MAE) of 13.35 mg/dL for PH = 30 min and 30.23 mg/dL for PH = 60 min.

3.3 Recommendation systems

A Recommendation system (RS) on self-management for diabetic patients must rely on a knowledge base of diabetes treatment and management. In order to explore guidelines based on general diabetes management, nutrition, diet and exercise, guidelines were collected from studies and authoritative public documents from internationally recognized associations in the context of diabetes. The emphasis in these guidelines is to provide information on the current state of the art on how to prevent and manage type 2 diabetes, with the goal of reducing complications and maintaining quality of life. This thesis focuses mainly on new information that has become available over the past 5-6 years.

Table 3.1: Summary of glucose prediction models found in the literature, where N is the number of subjects used in each database.

Study	Method	Database	PH (min)	RMSE (mg/dL)
Sparacino et al. [76] (2007)	AR	N=28, T1DM	30	18.78
			45	34.64
Pérez-Gandia et al. [77] (2010)	FFNN	N=6, T1DM	15	9.7
			30	17.5
			45	27.1
Zecchin et al. [81] (2012)	FFNN and first-order polynomial model	N=9, T1DM	30	14
Zecchin et al. [49] (2014)	JNN	N=10, T1DM	30	16.6
Ali et al. [78] (2018)	FFNN	N=13, T1DM	15	6.43
			30	7.45
			45	8.13
			60	9.03
Martinsson et al [79] (2018)	RNN-LSTM	N=6, T1DM (OhioT1DM Dataset)	30	18.87
			60	31.40
Sun et al. [53] (2018)	RNN-LSTM RNN-BiLSTM	N=20, T1DM	15	11.6
			30	21.7
			45	30.2
			60	36.9
Aliberti et al. [80] (2020)	RNN-LSTM	N=6, T1DM (OhioT1DM Dataset)	30	11.55
			45	19.86
			60	25
			90	30.95
Kim et al. [39] (2020)	RNN-GRU	N=20, T2DM	30	21.5

The general diabetes recommendations were drawn from multiple resources, such as the American Diabetes Association (ADA) through "Lifestyle Management: Standards of Medical Care in Diabetes 2019" [30] and "Standards of Medical Care in Diabetes-2022 Abridged for Primary Care Providers" [82], and lastly the "2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD" [35] was also reviewed. With more focus on recommendations regarding physical activity for these patients, the document "Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association" [3] was analyzed. For instance, [3] makes the following suggestion regarding the kind of exercise that individuals with T2DM should engage in: "Adults with type 2 diabetes should ideally perform both aerobic and resistance exercise

training for optimal glycemic and health outcomes."

Currently, many RS seem to provide users with useful wellness suggestions to engage in a certain activity that would improve their health, depending on their health status and body, knowledge derived from the users' past and other users similar to them. The systems found in the literature are mostly related to encouraging healthy eating, medication dosage, and promoting other wellness habits such as exercise. In this section we will cover some of the recommendation systems created for diabetic patients published since 2016.

In order to personalize the treatment of people with type 2 diabetes mellitus, Mahmoud et al. [83] created a recommender system, specific for medication. The approach incorporates rule-based decision-making, ontologies, and semantic web technologies while taking into account particular patient data, such as the individual HbA1c goal. A general guideline for choosing medications can be described as follows:

> "IF a patient is under 60 years old, suffering a liver problem, and used Sulfonzlureas (Glipizide), THEN starting dose should be 2.5mg daily."

Regarding dietary recommendations for diabetic patients, a system called DIETOS was created by Agapito et al. [84] and can offer dietary guidance to both healthy people and individuals who suffer from conditions such kidney failure, hypertension, and diabetes. The health profile was based on user responses to real-time dynamic medical questionnaires. By using this method, it is feasible to identify a user's health profile as monitored by a doctor and to give recommendations that are most appropriate for each user's health situation. In addition to recommending typical regional meals based on the user's health profile, DIETOS also displays nutritional information about each item recorded in the database, as well as its advantages and disadvantages with regard to particular pathologies and medical conditions. Still within the scope of diet management for diabetic patients, a mobile application was proposed by Norouzi et al. [85]. To aid with glycemic management and prevent hypoglycemic episodes, this application suggests snacks depending on the patient's preferences and current diabetes status. This application combines Artificial Intelligence (AI) techniques with a knowledge base constructed from the guidelines of the American Diabetes Association. One of the most important aspects taken into account when creating and modeling the application was patients' physical activity. In order to suggest the ideal snacks for users depending on their calorie needs, the authors used the Harries Benedict equation to quantify users' energy expenditure based on their degree of physical activity. Unfortunately, rather

than addressing the patients' conditions, this system was created with an emphasis on the patient's desires and BMI. The small sample size in the evaluation phase and omission of main meals are two additional drawbacks of the research. However, the quality of the recommendations can be improved with more accurate algorithms.

Additionally, more complex systems were found that give patients advice on multiple topics. A personalized recommendation system was given by Alian et al. [86] to assist American Indians in treating their diabetes. The recommender is based on the biocultural ontology of an American Indian user to enable personalization. The ontology served as the recommender's knowledge base, and general clinical diabetic recommendations and guidelines were transformed into rule-based logic. The proposed system was implemented as a prototype system and evaluated by use cases and expert verification. The device does not, however, track a diabetic patient's activities and does not have an interactive visual interface. In order to recommend the users with their diet, medication, and exercise, Bankhele et al. [87] suggested a recommendation strategy based on the CF technique. The system requires a patient to register before allowing them to provide a predetermined set of data, such as age, insulin, glucose, BMI, blood pressure, and triceps thickness. This information is compared to a database that has information on the history of people who have been diagnosed and treated, including the medications, food regimens, and exercise regimens that were employed. Once the parameters are matched and the closest user is found (using Pearson Correlation Score) the diet, medication, and exercise of the matched patient are retrieved from the database and are recommended to the user. Ali et al. [88] developed a hybrid framework that also provides physical activity, dietary and educational recommendations to a selected target user group. This is achieved using context- and knowledge-based recommendations. The proposed model is based on IF-THEN rules, which are then adopted to create recommendations. For example:

> "IF a patient is pregnant and facing the gestational diabetes mellitus, THEN she should do a 20-30 minute moderate-intensity exercise on almost every day of the week." [3]

There are two parts to the recommendation process. In Phase 1, the system determines the user's calorie burn, dietary goals, and a general list of suggested physical activities. To further deduce the most pertinent rules from the knowledge base, a case-based reasoning method is used. Phase 2 involves a tailored refinement of the recommendations made in phase 1. To suggest activities suitable for the user at a specific time, a contextual matrix is constructed. This matrix is created based on the results of the user's survey in order to suggest the appropriate physical

activity in various situations. For example, "since the user is now staying at home, stretching seems to be more appropriate for him than running".

The table 3.2 summarizes the above mentioned recommendation systems. The system in question is described and the platform it is on. The type of recommendation system used and the technologies used are listed, as well as the type of recommendations it provides.

Table 3.2: Summary of recommendation systems created for diabetic patients published since 2016.

Study	Name of the system (System Platform)	Type of RS	Type of AI techniques applied in RS	Functionalities
Mahmoud et al. [83] (2016)	IRS-T2D (Unspecified)	Knowledge-based recommender systems	Domain Ontology, Semantic Web Rule Language (SWRL)	Medicine recommendations
Agapito et al. [84] (2018)	DIETOS (Web Application)	Knowledge-based recommender systems	–	Food recommendations
Norouzi et al. [85] (2018)	Iranian Snack Recommender System (Mobile Application)	Knowledge-based recommender systems	Rule base	Food recommendations
Alian et al. [86] (2018)	– (Mobile Application)	Knowledge-based recommender systems	Domain Ontology, Semantic Web Rule Language (SWRL)	Physical activity recommendations Diet recommendations
Bankhele et al. [87] (2017)	– (Mobile Application)	Collaborative filtering recommender systems	Rule base	Physical activity recommendations Diet recommendations Medicine recommendations
Ali et al. [88] (2018)	– (Unspecified)	Hybrid recommender systems	Rule base	Physical activity recommendations Diet recommendations Educational recommendations

3.4 Concluding remarks

There is already a big market of mobile applications oriented towards the self-management of T2DM. These offer a variety of features, being able to connect to wearable devices to record and track BG levels, physical activity, caloric intake, and HbA1c (among others) to offer feedback, recommendations and reminders that have been proven to have positive results in the life of patients. However, further research is needed to assess what the long-term benefits of mobile application-based interventions, while continued efforts must be made to develop increasingly personalized mobile applications. Since diabetes can have a negative psychological impact on patients, it is also important to analyze how these technologies can improve this aspect. It is still necessary to bridge the gap between the scientific literature and the applications actually developed and launched on the market. More research is critical in developing the next generation of mobile health systems that will enable

the wider use and clinical acceptability of these innovations in the future of digital diabetes management and treatment systems.

In recent decades, several technological developments have been incorporated into blood sugar level prediction. Several algorithms such as autoregressive time series models and Machine Learning (ML) have already proven to achieve good accuracy values in short-term prediction of diabetes. Nevertheless, more studies are needed in long-term prediction focused on patients with type 2 diabetes.

Regarding recommender systems, the majority of the studies that were discovered were focused on enhancing users' wellbeing by suggesting diets and exercise regimens. However, a significant number of writers have put work into creating systems that can assist doctors in the process of diagnosing, treating, and prescribing drugs. Despite all the work that has been done in recent years, this field of study is still in its early stages, necessitating more extensive investigation. Health-related issues are complicated, and today's health recommendation systems don't have a single solution for all of their challenges. We may infer from the research articles examined and our perspective that we still have a long way to go before we have a trustworthy and fully operational health recommendation system. Moreover, efforts should be made to address the ambiguity that comes with health-related decision-making and define more suitable testing procedures that allow the accuracy and effectiveness of implementations to be adequately assessed.

Therefore, taking as a starting point the studies discussed in this chapter, this thesis will develop two modules that will be incorporated into the POWER project (whose objectives were described earlier). Besides solving a problem for our main partner (Altice Labs) we intend to contribute with innovative models in comparison with past literature. With the development of the prediction module, we aim to deepen the literature concerning the prediction of future glucose values for patients with type 2 diabetes. In addition, we focus on long-term predictions that mirror the consequences of patient actions, which to our knowledge have not been explored so far. Regarding the recommendation module, in addition to recommendations based on general guidelines, it will contain a personalized component for each patient. The existence of the prediction, besides alerting the patient of the existence of possible dangerous glucose peaks, will provide those values to the recommendation module. Then, based on the predicted future glucose values, it can suggest lifestyle modifications for the patients. These when taken should prevent the predicted peaks from being reached and thus help in managing the glucose value in the healthy range.

4

Experimental Setup

This chapter aims to describe the methodologies used to implement the models for both modules. The Section 4.1 starts by describing the database used to validate the implemented models. Next, its pre-processing and framing are detailed to prepare the input data for the data-driven models. The construction and optimization of the implemented models are also explained. The section ends with an indication of the evaluation metrics used to compare the models. In Section 4.2, it is presented how the knowledge was acquired for the Knowledge-Based Recommendation System (KBRS) and how the rules for its implementation were generated. Section 4.3, which ends this chapter, indicates the need for the creation of an Application Programming Interface (API) with the final models of each module as one of the requirements of this project.

4.1 Prediction module

In this section, we go through how the prediction model was created to forecast future glucose levels over various Prediction Horizons (PHs). Such a model can prevent patients from developing abnormal glucose levels since it allows us to notify patients before their blood sugar levels overcome specific thresholds, allowing them to take preventative actions to avoid potentially dangerous situations.

4.1.1 Methodology

In order to create a model that is able to predict the glucose level in advance, there are certain steps that need to be followed, which are schematically shown in Figure 4.1. The process begins with the data collecting phase, where access to the problem-related data is mandatory. Pre-processing the information is the next stage since the model might not be able to manage any irregularities it contains. In the data framing stage, the data is adequately framed to fit into the models. The chosen algorithms are implemented in the following phase. Several tests should be run at

this point to evaluate the model's quality. Eventually, it could be required to adjust the model's parameters, test those modifications, and assess how well they work. The final model is adopted when there are no more improvements that can be made and/or the outcomes are satisfactory.

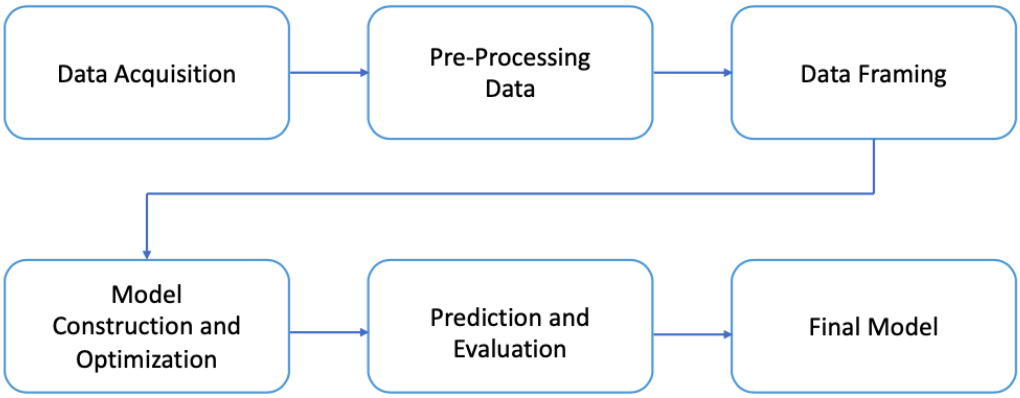


Figure 4.1: Steps integrating the prediction module. It should be noted that the steps in this scheme can be redone and improved when necessary.

4.1.2 Data Acquisition

To achieve the goals set earlier, we need a dataset to validate the model developed. However, because this is a time series problem, the dataset employed here has a special property: the records have a temporal link between them.

In the present work a dataset provided by Associação Protetora dos Diabéticos de Portugal (APDP), with real patient data, was used to validate the models implemented. Blood sugar levels were recorded in free-living conditions using the Medtronic iPro2 CGMs with a 5-minute sampling period. The records (i.e., Continuous Monitoring Device (CGM) time-series) containing the blood glucose concentration levels were collected as part of an observational research that included adult participants with type 1 diabetes mellitus and adult participants with type 2 diabetes who were receiving hemodialysis. The duration of the CGM time-series ranged from 2 days to 8 days, had cutoffs for values below 40 mg/dL and above 400 mg/dL, which corresponds to the sensor range, and may include several periods of missing data. Numbers below 70 mg/dL are established as hypoglycemia and above 180 mg/dL as hyperglycemia.

For the experiments, anonymized data from 10 subjects were selected from the larger dataset based on the following criteria: 1) Have type 2 diabetes mellitus, 2)

Participate in two experiments. Following the selection criteria, we derived the new dataset that includes 10 Type 2 Diabetes Mellitus (T2DM) subjects, each represented by variable sizes of the CGM time series (later undergoing preprocessing). Descriptive statistics for the selected subjects are presented in Table 4.1, and an overview of the CGM profiles is presented in Table 4.2.

Table 4.1: Descriptive statistics of the dataset.

Characteristic	**Mean ± SD**
Gender	5F / 5M
Age (years)	73.7 ± 7.4
Diabetes duration (years)	16.7 ± 8.2
Body Mass Index (BMI) (kg/m2)	31.8 ± 2.8
Fat mass (%)	44.0 ± 5.1
Hemoglobin A1c (HbA1c) (%)	7.4 ± 1.8

Table 4.2: Glucose profile statistics of the dataset per trial.

	Trial No.1	**Trial No.2**	**Total**
Average glucose concentration (mg/dL)	175.8 ± 58.3	163.8 ± 40.7	169.8 ± 49.5
Minimal glucose concentration (mg/dL)	63.9 ± 19.1	52.4 ± 17.2	58.1 ± 18.1
Maximal glucose concentration (mg/dL)	310.7 ± 99.1	322.4 ± 70.1	316.5 ± 84.6
% hypoglycemic values (≤70 mg/dL)	2.7 ± 5.2	3.1 ± 2.4	2.9 ± 3.8
% values in healthy range	55.9 ± 32.7	62.3 ± 24.6	59.1 ± 28.7
% hyperglycemic values (≥180 mg/dL)	41.4 ± 34.5	34.5 ± 25.6	38.0 ± 30.0

4.1.3 Pre-processing

A dataset is a collection of observed variable values that were either manually or automatically gathered. As a result, there may be noise and/or missing information, making pre-processing an essential step to address this issue. In this stage, records that have missing values are fixed or removed, new features are calculated since certain algorithms do not accept them, the data is normalized, etc.

Missing values

After examining the APDP dataset, we verified that it was not complete, that is, that there were gaps (missing values). There are at least two options to solve this problem, which are the following: i) data deletion or ii) imputation. However, it is not advisable to rely on the first alternative because health information is extremely difficult to find and databases often include a small number of entries. Additionally, since those records could be different from the remaining ones without the removed instances, the model's capacity to generalize is likely compromised.

The second alternative seeks to substitute missing data with an estimate of their values. Such a replacement can be done, for instance, using one of the following approaches: Random value, Average of the k-nearest neighbours, Feature's class median or Feature's class mean.

We analyzed all data and verified that excluding the beginning and the end of the measurements (which had lack of measurements for a period), no more than one value was missing consecutively. We also found that besides the feature corresponding to the registration of glucose values measured by the CGM device there was another feature corresponding to manual measurements. In multiple cases when a value was missing in the column corresponding to the automatic measurement there was a measurement performed manually. Therefore, three strategies were used to deal with the missing values in this dataset:

1. The initial and final segments that corresponded only to several missing values were eliminated;
2. When there were manual measurements (originating a missing value in the records mesured by the CGM sensor), their value was placed in the corresponding position of the automatic measurement;
3. The remaining missing values were calculated through imputation of the average of the previous and next value (since they were single values and the previous and next value are only 5 min apart from the missing value).

Normalization

Normalization of the original data can improve the distribution of the data and speed up the learning of the model to a certain extent. The two commonly used standardization methods are min-max standardization and Z-score standardization. The first method guarantees that all features will have the same scale, but does not handle outliers well. Z-score normalization, on the other hand, deals with outliers but does not produce normalized data with the same scale.

The goal of this step was to scale the values within a predefined limit, namely [-1,1], without losing the inherent information. For this purpose, we used data scaling based on min-max normalization - see Equation 4.1, where X denotes the original value of the feature of interest, X_{min} corresponds to the minimum value of the feature, X_{max} denotes maximum value of the feature, and R the desired range of the scaled features [89]. In this case, it is possible to use this method, since the glucose level can range from 40 to 600 mg/dL (exposure above this value in a prolonged manner can lead to hyperosmolar hyperglycemic syndrome [90]). Nevertheless, to ensure that no new values appear, this range was extended by setting the minimum

possible at 20 and the highest at 800 mg/dL.

$$\bar{X} = \frac{(X - X_{min})}{(X_{max} - X_{min})} \qquad X_{scaled} = \bar{X}(R_{max} - R_{min}) + R_{max} \tag{4.1}$$

4.1.4 Data framing

After pre-processing the data, for its use in the algorithms, there is a need to organize the information in the appropriate format. In order to predict future glucose values taking into account only the patient's CGM history, we started from the ideal scenario to a possible one, which led us to create two approaches.

The first approach, and ideal, consists in using all the continuous CGM values to perform a prediction in the different PHs. However, as we will see below, this approach becomes difficult to implement for the chosen time horizons. Therefore, a second approach was used, where instead of looking at continuous values, the data is transformed so that its trends can be identified. This is accomplished by grouping the patient's CGM information into blocks every 2h, i.e., since the CGM records the values every 5 minutes, it is made an averaged every 24 values (corresponding to 2h). Other values were considered for the size of the blocks that are grouped by averages, however, in discussion with the project partners, it was concluded that 2h would be the most suitable.

As mentioned in Section 2.2.1, the input to the prediction models (regardless of which approach is used) is framed as a supervised learning problem using the sliding window method. For this, some parameters have to be stipulated, like the PH and lookback values. The windowing step remains one sample, as stated before.

Since this thesis is part of a funded project, there are some requirements discussed in collaboration with the partners involved. The different values of the prediction horizon were one of the parameters under discussion. As the purpose of the algorithm is to predict glucose values for T2DM patients, longer values of PHs such as 2h, 4h, 12h, and 24h were defined. These reflect the consequences of patients' actions, like eating a meal or doing physical activity, to create conditions for developing recommendations that have an impact on users' lives.

Another requirement of this research, to make this module more flexible, was that there should be several versions of the final model, prepared to be able to perform predictions even with insufficient data. Therefore, there are several lookbacks per PH, and one of them is indicated as the optimal one, which achieves the most satisfactory values by the chosen evaluation metric. Other lookbacks guarantee an

acceptable prediction, but with inferior results. This means that the model is previously trained for several scenarios (for different lookbacks). So, even if the optimal lookback is not guaranteed as input by the end user, the final model is prepared to receive less data and still perform the predictions. However, a minimum amount of data is required, otherwise the model does not perform the prediction and alerts the user with an specific error code (these details are explained in the API developed for this module which will be explained later).

The lookback value then became a hyperparameter of the models. A grid search was conducted to identify which lookback is optimal for each PH. The grid search is a tuning method that seeks to determine the optimal hyperparameter values. It is an exhaustive search that is performed on the specific parameter values of a model. When an evaluation of all possibilities is made, it offers the combination that creates the highest value of the scoring metric that was previously specified when iterating through every parameter option and storing a model for each one.

4.1.5 Model construction and optimization

The prediction module was built with the high-level neural networks API Keras version 2.7.0 in the Python 3.9.7 environment. Six prediction models were implemented to determine the best one for the task of blood sugar level prediction. The selected algorithms were Autoregressive Integrated Moving Average (ARIMA), Case-based reasoning (CBR) and four neural networks: Recurrent Neural Network (RNN), Gated Recurrent Unit (GRU), Long Short-Term Memory (LSTM) and Jump Neural Network (JNN), since they stood out in the literature review for better performance compared to other models.

All implementations were based on parameters and model specifications described in the models found in the literature. Actually, we present the identified and reimplemented state-of-the-art models, a CBR [43] and JNN [49], respectively, as reported by the authors. The remaining models, meanwhile, were subject of brief grid searches in order to optimize some hyperparameters.

Hyperparameter optimization is the process of choosing a set of optimal hyperparameters that maximize the performance of the model. For this purpose, a brief tuning of the predictive models was performed to obtain the appropriate hyperparameters for the input data and the purposes of the model application.

Regarding the ARIMA model, the literature has traditionally used the autocorrelation and partial autocorrelation function plots to estimate the p and q parameters' respective ranges. A grid search approach may then be used to determine

the exact values of the p and q parameters using this range. However, since this procedure may be extensive and time-consuming, AutoARIMA is able to automate it. Different tests (i.e., Kwiatkowski–Phillips–Schmidt–Shin, Augmented Dickey-Fuller or Phillips–Perron) are run to determine d, and the optimal model is chosen based on having the lowest Akaike Information Criterion (AIC) fitting several models within a given range for p and q. In practice, AutoARIMA is implemented by the pdmarima Python module and models are fitted using Newton's method [40].

The proposed CBR model described in [43] was implemented. All the steps described in the proposed method were followed, so we suggest the reader to analyse the point regarding Methods from the original article for a better understanding. As in [43], we omitted revision and retaining steps to remove the complication of the input subject's own data during the training and prediction task, for a fair comparison with the other models. The original paper used time horizons equal to 30 min and 60 min while in this thesis, as mentioned earlier, longer time horizons were chosen. The distance function, the number of similar cases used (K) and the adaptation function were considered as the hyperparameters of the CBR model. Zulj et al. [43] stated that for the chosen configuration, the considered choices of the hyperparameters did not contribute substantially to the improvement of the prediction. Thus, and since the goal of this work is not to find the optimal parameters for glucose prediction using the CBR model, we used the hyperparameters that gave the best results in the study, except for the selected number of cases K (since our study had fewer cases than the original). So, we used the 'cosine' distance function, the Linear Regression (LR) adaptation function, and for the value of K a brief search was made to identify the best value. In order to reduce the possibilities that could be tested for this parameter, we evaluated the values of K equal to 50, 100, 150 and 200, for the three time horizons.

Relatively to the neural network models, the JNN proposed in [49] was implemented. Four neurons were used in the hidden layer and as input only the blood glucose concentration values were considered, disregarding the input absorption model. The implementation with this limitation on input was performed by the same author in [91]. Thus, for a detailed description of the network architecture, we would like to refer the reader to the appendix found in the original paper [91]. For the remaining neural networks, all implementations consisted of a single hidden layer. In [39], RNN, GRU and LSTM networks were also implemented on T2DM patients and the results showed that as layers increased the performance of the models decreased. In each network 50 units were used in the hidden layers. A dense layer of one unit was also used to produce the final predicted blood glucose

value. The rest of the network parameters were selected from a grid search. Table 4.3 describes the settings of the RNN, GRU and LSTM to be optimized: number of epochs, batch size, optimization function, loss function and learning rate.

Table 4.3: RNN, GRU and LSTM hyperparameters settings for grid search.

Hyperparameter	Settings
Number of epochs	100, 200, 300, 400, 500
Batch size	8, 12, 16, 20, 24, 28, 32
Optimization function	ReLu, Tanh, Sigmoid
Loss function	RRMSE, MSE
Learning rate	0.1, 0.01, 3e − 3, 3e − 4, 3e − 5, 3e − 6

4.1.6 Evaluation metrics

To help us compare the results of a model against another one some metrics were calculated. The evaluation metrics used in the context of glucose prediction, for empirical accuracy, are usually: Root Mean Square Error (RMSE) (Equation 4.2), which is the standard deviation of the residuals (a measure of how far the data points are from the regression line) and Mean Absolute Percentage Error (MAPE) (Equation 4.3), which is one of the most common measures used to predict error, probably because the variable's units are scaled to percentage units, which makes it easier to understand.

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\hat{y}_i - y_i\right)^2} \tag{4.2}$$

$$MAPE = \frac{1}{N}\sum_{i=1}^{N}\frac{|\hat{y}_i - y_i|}{y_i} * 100\% \tag{4.3}$$

where $\hat{y}$ is the predicted time-series, y the target time-series and N is the length of the time series. So $\hat{y}_i$ (mentioned before as $\hat{x}_{n+PH}$) and y_i are the predicted and actual blood glucose values respectively.

To measure the clinical accuracy of the models' predictions the Clarke Error Grid (CEGA) is used. Errors are divided into zones in this grid system, and each zone is made up of a range of reference and forecast values. On the error grid, the correspondence between real and predicted blood glucose levels is displayed. Each of these pairs falls into one of the error grid zones. Each zone represents the degree of risk of a result resulting from the difference in error between predicted and actual values. CEGA is accepted as one of the "gold standards" for assessing the accuracy of blood glucose meters [78].

The CEGA provides a clinical interpretation of the mapping between predicted and measured blood glucose levels, that can be represented in a scatterplot with five main regions [73] (see Figure 4.2).

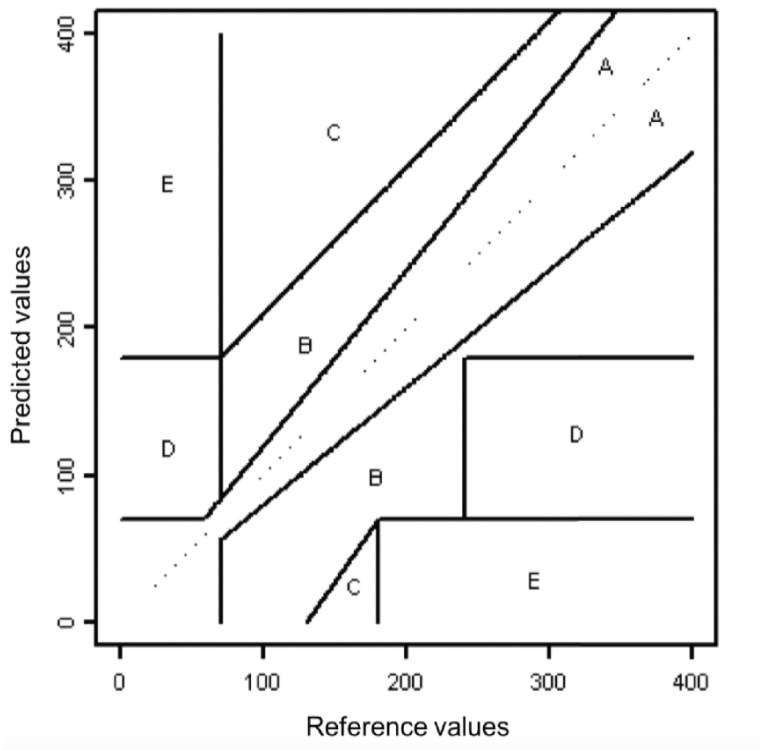


Figure 4.2: Clarke error grid analysis: Reference regions mapping. From [73].

Its five zones are described bellow [73, 78]:

Zone A: characterizes the predicted blood glucose levels that are deviated from the actual blood glucose levels by no more than 20% of the reference sensor;

Zone B: characterizes the predicted blood glucose levels that are outside of 20% of the reference sensor but would not lead to inappropriate treatment;

Zone C: values leading to inappropriate treatment, but without dangerous consequences for the patient;

Zone D: characterizes dangerous cases to identify and to assess significant clinical mistakes and errors;

Zone E: values leading to treat hypoglycaemia instead of hyperglycaemia and vice-versa (wrong medication adjustment).

The model's performance may be better evaluated by having more pairs of predicted and actual points appearing in Zone A [92]. In terms of clinical usage, a higher percentage of results falling within zones A and B denotes a more accurate result.

4.2 Recommendation module

In this section, it is seen how the KBRS was created and implemented through a Rule-based system (RBS). The success of diabetes control is greatly influenced by self-care techniques and behaviors since daily diabetes care is predominantly managed by patients and their families. Therefore, this module allows patients to obtain recommendations on their lifestyle habits that can guide them towards a healthier life and greater control over their disease.

4.2.1 Methodology

In order to create a recommendation system, it is essential to gather knowledge about the problem at hand from reliable sources. After the intensive search for diabetes guidelines and their selection according to the project requirements, it is then necessary to translate this information into rules that can be used by the model to deliver the recommendations to the patients. After all the rules are defined, they are implemented and the model is built. Figure 4.3 depicts the steps needed to create this system.

Figure 4.3: Steps integrating the recommendation module. It should be noted that the steps in this scheme can be redone and improved when necessary.

4.2.2 Knowledge acquisition

As mentioned in Section 3.3, guidelines based on general type 2 diabetes management, diet and nutrition, and physical training were systematically explored. At this stage of the project, the only source of knowledge resulted from authorized public documents made available by international diabetes-related associations. In a future step, a team of endocrinologists will verify this knowledge and complement it by creating guidelines using the values obtained from the prediction module to provide a personalized recommendation system.

From all the available guidelines in the documents referred to in Section 3.3, those that, after discussion with the project partners, fulfilled the following criteria were selected: 1) Fall within guidelines on general management, diet and nutrition or physical exercise of type 2 diabetes; 2) Use variables that are possible to be entered by patients; 3) Present measurable variables. The chosen guidelines can be found in Appendix A.

4.2.3 Rule generation

After knowledge acquisition, through the guidelines, it was necessary to convert it into rules that can be handled by a computer. The recommendation module was built with in the Python 3.9.7 environment. Firstly, it was required to decide on the input and output variables of the system as well as their respective domains. After that, we opted for the most popular *"premise→conclusion"* logic form to create the rules. In this format, these can be understood as IF-THEN clauses, explained earlier in section 2.2.2. The *premise* of this logical form can be defined by the logical conjunction of a set of logical expressions. Each logical expression is constructed based on logical operators to link variables representing the real-time disease context of users (such as current glucose value, predicted value in a specific PH, the tendency of glucose levels, etc) and users personal data (such as sex, age, comorbidities, etc). A user when making a record, by assigning values to the different input variables, allows the evaluation of the conditions expressed within these logical expressions. The possible *conclusion* may be the indication of decreasing, maintaining or increasing an action as a recommendation, for example, it may be indicated to increase the number of minutes per week of exercise.

4.3 Application programming interfaces

As this thesis is integrated in a project in which the purpose is to develop and deliver to our partner the produced modules that will be integrated in the respective platform, it is necessary to develop an API for each module. These interfaces contain the final models of the prediction and recommendation system, as well as a module for processing the acquired data. In practice, the acquired data will come directly from sensory devices, e.g. CGM and mobile phone, and will therefore require format validation and consequent pre-processing.

5

Results and Discussion

This chapter presents the main results of this research. The Section 5.1, concerning the prediction module, reports the results of the grid search for the best hyperparameters and presents the forecasting results, for the established prediction horizons, on the test set for each implemented model. In addition, the mean values and standard deviations of the evaluation metrics are tabulated and discussed. Regarding the recommendation module, the results are described in the Section 5.2. First, the input and output variables chosen for creating the Rule-based system (RBS) are specified. Then, the rules created to offer recommendations to users are described. The chapter ends with Section 5.3 where the developed functions used in the Application Programming Interface (API) created for the project are specified, based on the results obtained.

5.1 Prediction module

5.1.1 Input data for data-driven models

To deal with the problem of predicting future glucose values only Continuous Monitoring Device (CGM) data was used as input. These are recorded by the CGM device every 5min. When establishing long prediction horizons such as 2h, 4h and 12h it becomes decisive to use as input data, sequences at least equal to or longer than the prediction horizons. When performing the tests for tuning the hyperparameters (described in the next section) some difficulties arose in the task. Using all measurements continuously to determine only one exact value after a few hours becomes very demanding for the model. As mentioned before, the dynamics of glucose are complex and depend on several factors such as diet, exercise, hormonal values, psychological stress, etc. In the literature, as described in Chapter 3, we found several studies that can make this prediction quite accurately for Type 1 Diabetes Mellitus (T1DM) patients, despite only existing researches for short time horizons (rarely exceeding 1h). However, for longer horizons where, with the passage

of time, the intervention of the factors mentioned above settles down and it becomes difficult to achieve satisfactory results. Therefore, since the goal of this study is to predict and then make inferences about the lifestyle habits of Type 2 Diabetes Mellitus (T2DM) patients, a second approach can be created to input the data into the models. This one aims to prioritize glucose trends rather than its exact value, which is the most important for the recommendation module. Here, the crucial point is not to tell the patient the exact glucose value within 4h, but to be able to predict whether the blood sugar value will tend to rise or fall to dangerous values so that recommendations can be made when taken by the patient will prevent this outcome.

To illustrate and better understand the second approach, the Figure 5.1 contains two plots for the same patient and the corresponding CGM record. The upper figure shows the continuous register and the lower figure shows the transformed one by the second approach method. In this, the points of the CGM record were grouped by the average every 24 points, corresponding to every 2h. By analyzing both figures it is possible to see that the trends of increasing/decreasing glucose values are preserved. It is emphasized that since the aim is to infer about the lifestyle habits of T2DM patients and not of T1DM patients (who due to their dependence on insulin and medication need continuous and rigorous predictions) this approach is feasible.

It should be noted that, in what remains of this chapter, all the results presented are relative to the implementation of this second approach.

5.1.2 Hyperparameters selection

To create more reliable and effective models when applied to our dataset, we tried to optimize the developed models by tuning some hyperparameters. The look-back value assigned to each forecast horizon was one of the hyperparameters chosen to be tuned. Moreover, some specific parameters of the models were subject to grid searches.

Naturally, different hyperparameter choices were made for the different training sets and different models. However, to establish a final design for each model, the most appropriate choices correspond to the most frequently determined values. To facilitate comparison between the developed models and to reduce the amount of testing in tuning the hyperparameters, the choices that were most frequently connoted as the best for the lookback value of each Prediction Horizon (PH) were used in all models.

In order to proceed with the hyperparameter optimization the leave one out

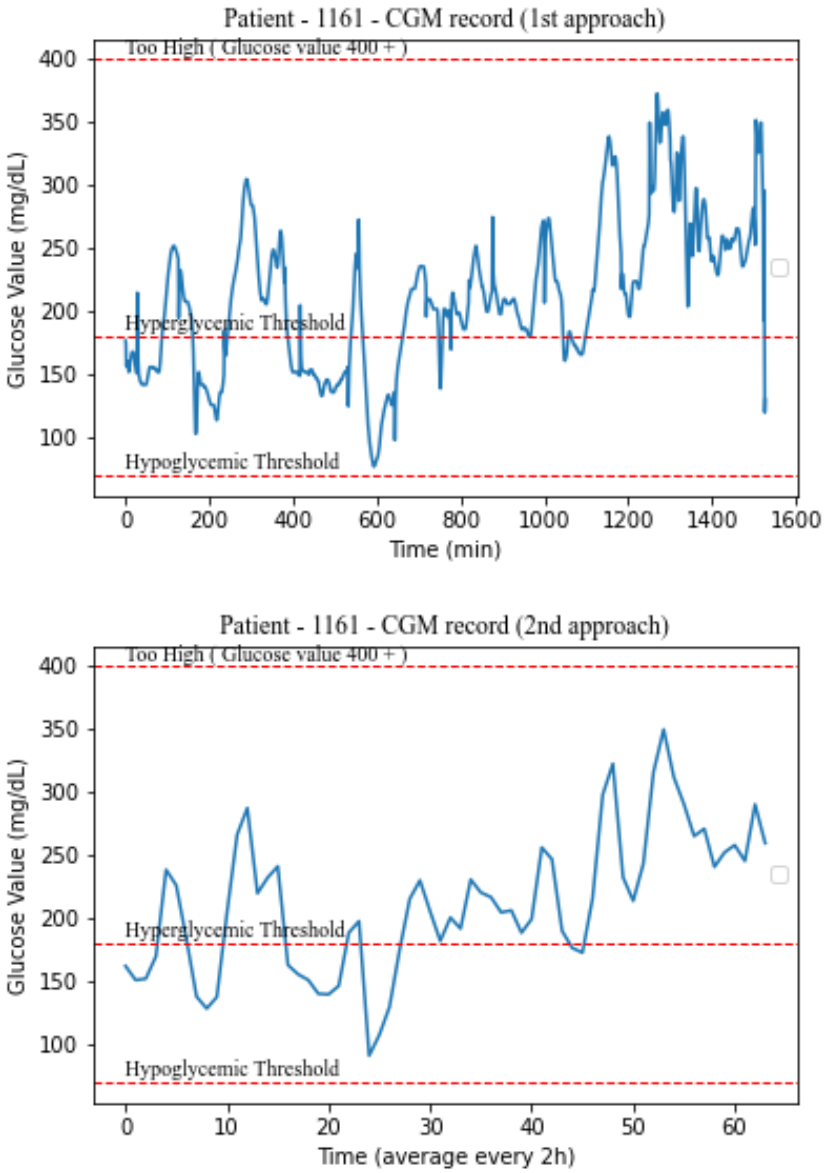


Figure 5.1: Example of the transformation of the first trial (indicated by the last 1 in the patient code) of patient 116 data from the first approach to the second approach. In the upper graph is the CGM record without change. The lower graph shows the data grouped by the average every two hours.

cross validation method was used, i.e., the learning algorithm is applied once for each patient, using all the other patients as a training set and using the selected patient as an individual test set.

Selection of ideal lookback per PH

A grid search was carried out in order to obtain which lookback is ideal per PH, i.e., the one that, using the selected evaluation criteria, produces values that are the most satisfactory. For PH=2h, lookbacks equal to 2h, 4h, 6h, 8h and 12h were tested, and the one that achieved the best results was 12h. For the remaining PHs were tested lookbacks equal to the PH, twice the PH, and three times the PH. For 4h and 12h, the top performing lookbacks were 12h and 24h, respectively. It should be noted that lookbacks longer than 36h were not considered, since the longer the lookback, the fewer points would be used in the prediction, which would falsely lead to lower error values.

When conducting this search, we realized that the 24h time horizon is not feasible. Firstly, in a 24-hour interval, the patient can perform numerous actions that affect glucose values. During this period several meals are eaten and more than one training session can be performed (considering that, for example, a patient can train one day in the evening and the next day in the morning). Furthermore, it is difficult for models to find similar patterns over such a long horizon due to the heterogeneity associated with the patient's day-to-day routine, i.e., a day at work is different from a day off or a more stressed day at work. These factors make the forecast for this PH very unreliable. Additionally, more input days would be needed to try to improve the performance of the models in this horizon, however, and as already mentioned, since the dataset is not very extensive using long periods as input leads to falsely positive results.

So, table 5.1 illustrates a example of how the data is framed for the forecast. For a forecasting horizon of 4h, i.e., to forecast the 48th value after the last input value, to achieve the result with the highest degree of confidence, 12h of input (144 values) are needed. Using the remaining lookbacks (4h and 8h) will, most likely, generate least accurate results. For the implemented approach, explained above, the same logic is used. To predict the average of two 2h block after the last input value, the averages of 6 previous 2h blocks (12h) are needed as inputs.

Table 5.1: Form of the input sample. Example where x is a CGM time series with the values grouped by the average every 2h, where the lookback corresponds to 12h and PH=4h.

Input values					**PH**	**Target value**
x_1	x_2	x_3	...	x_6	...	x_8
x_2	x_3	x_4	...	x_7	...	x_9
x_3	x_4	x_5	...	x_8	...	x_{10}
...						

Models Settings

When implementing the Case-based reasoning (CBR) model described in [43], we realized that we only had 1178 *cases* available, while the original model had 25,590 *cases*. The definition of a *case* is described above in Section 2.2.1.2. So it was not possible to use the same range of values for K (number of similar cases used for prediction) as the authors. We preformed a little research on what value to use for our dataset. The results of this grid search are shown in Table 5.2. The other two parameters, as mentioned earlier, corresponded to the cosine distance function and the Linear Regression (LR) as adaptation function.

Table 5.2: Grid search results for the K value of the CBR model.

PH	**K**	**RMSE (mg/dL)**
2h	50	37.39
	100	36.11
	150	35.94
	200	**35.64**
4h	50	50.17
	100	48.43
	150	48.43
	200	**47.95**
12h	50	55.90
	100	53.79
	150	53.37
	200	**51.83**

Therefore, as in the original paper, it is found that the performance improves as the value of K increases. The hyperparametric choices for the model are given as a triple (adaptation function, distance function, K). Since K=200 was the one that obtained the best results for all three time horizons, we can represent the final model as CBR(LR, cosine, 200).

Another grid search was used, in this case to identify the optimal Recurrent

Neural Network (RNN), Gated Recurrent Unit (GRU) and Long Short-Term Memory (LSTM) hyperparameters. Although it was not the goal of the study, we could have looked at the best model parameters in more detail. Only a little fine tuning was done to ensure that the parameters were selected with a minimum of confidence and were not chosen at random. Table 5.3 shows the results of the grid search performed for the three neural networks. This shows the most common parameter choices among the different training sets used.

Table 5.3: Grid search results for the RNN, GRU and LSTM hyperparameters.

Hyperparameter	**Most common option**
Number of epochs	300
Batch size	8
Optimization function	ReLu
Loss function	MSE
Learning rate	$3e-5$

Future research should focus on the issue of picking the best hyperparameters model and determining how much historical data on glucose levels should be used to estimate future values.

5.1.3 Glucose prediction

The Autoregressive Integrated Moving Average (ARIMA), CBR, RNN, GRU, LSTM and Jump Neural Network (JNN) methods were used to predict the next blood glucose levels for prediction horizons of 2h, 4h and 12h, using the ideal look-backs already stipulated. The presentation and discussion of the results was divided into two points to promote an evaluation of the applied methods as complete as possible. i) Analytical evaluation: where results are presented for a set of statistical indices widely used in the literature to validate the predictions from the point of view of regression analysis; ii) Clinical evaluation: the results of metrics specifically designed to validate the clinical outcome of blood glucose measurements are presented to validate the predictions from a clinical point of view.

Analytical evaluation

Root Mean Square Error (RMSE) and Mean Absolute Percentage Error (MAPE) were used to quantify the similarities between the predicted and observed time series. The subjects in the Associação Protetora dos Diabéticos de Portugal (APDP) dataset were randomly divided into two subsets: a training set consisted of the data from 7 subjects (14 trials), and a testing set with the data from the remaining 3 subjects (6 trials). We show results individually for both trials, per patient (marked

with an identification code 102, 106 and 116) and averages in predicting glucose levels.

Tables 5.4 and 5.5 report the experimental results obtained by running the final models for PH=2h, using 12h as lookback, evaluated by RMSE and MAPE, respectively.

Table 5.4: Comparison of the performance for PH=2h – RMSE.

RMSE (mg/dL) - PH=2h							
Subject ID	**Trial No.**	**ARIMA**	**CBR**	**RNN**	**GRU**	**LSTM**	**JNN**
102	1	26.81	22.89	22.74	23.75	23.71	24.67
102	2	45.28	40.19	41.64	41.02	41.09	43.36
106	1	50.11	36.85	34.43	35.42	35.68	37.04
106	2	44.63	31.87	30.68	30.71	30.84	33.20
116	1	46.84	33.46	32.76	32.54	32.58	32.37
116	2	66.01	48.75	46.68	47.74	47.87	51.91
	Mean	46.61	35.67	34.82	35.20	35.29	37.09
	SD	11.45	7.91	7.69	7.63	7.67	8.67

Table 5.5: Comparison of the performance for PH=2h – MAPE.

MAPE (%) - PH=2h							
Subject ID	**Trial No.**	**ARIMA**	**CBR**	**RNN**	**GRU**	**LSTM**	**JNN**
102	1	18.01	17.30	16.03	16.38	16.41	16.97
102	2	28.08	25.88	27.49	26.50	26.31	27.01
106	1	24.32	17.71	17.03	17.42	17.56	18.20
106	2	20.31	16.27	16.02	15.99	15.20	16.66
116	1	19.60	12.98	13.47	13.06	12.87	12.96
116	2	29.14	19.40	19.92	19.77	19.90	21.38
	Mean	23.24	18.26	18.33	18.19	18.04	18.86
	SD	4.26	3.92	4.51	4.21	4.27	4.41

Tables 5.6 and 5.7 report the experimental results obtained by running the final models for PH=4h, using 12h as lookback, evaluated by RMSE and MAPE, respectively.

Tables 5.8 and 5.9 report the experimental results obtained by running the final models for PH=12h, using 24h as lookback, evaluated by RMSE and MAPE, respectively.

The ARIMA model was implemented as a baseline. It was noted, at all time horizons, that the machine learning models outperformed the traditional model.

Table 5.6: Comparison of the performance for PH=4h – RMSE.

RMSE (mg/dL) - PH=4h							
Subject ID	**Trial No.**	**ARIMA**	**CBR**	**RNN**	**GRU**	**LSTM**	**JNN**
102	1	26.75	27.89	27.15	25.84	25.36	27.63
102	2	49.99	50.40	49.20	48.85	48.04	48.49
106	1	56.87	48.91	47.13	47.55	47.16	49.35
106	2	54.79	44.11	41.75	42.02	44.78	47.64
116	1	56.08	47.27	47.73	46.90	48.46	47.16
116	2	76.15	69.97	66.59	67.73	69.28	70.43
	Mean	53.44	47.97	46.59	46.48	47.18	48.45
	SD	14.50	12.09	11.62	12.27	12.73	12.38

Table 5.7: Comparison of the performance for PH=4h – MAPE.

MAPE (%) - PH=4h							
Subject ID	**Trial No.**	**ARIMA**	**CBR**	**RNN**	**GRU**	**LSTM**	**JNN**
102	1	17.87	20.88	19.12	18.62	17.91	19.36
102	2	31.71	32.27	31.66	31.06	30.61	29.03
106	1	29.51	24.21	24.09	24.46	24.33	25.33
106	2	27.78	23.06	22.35	22.14	23.49	23.75
116	1	24.05	17.96	19.51	19.40	19.59	19.06
116	2	34.80	30.14	29.37	31.19	32.23	31.70
	Mean	27.62	24.76	24.35	24.48	24.69	24.70
	SD	5.47	5.00	4.71	5.06	5.25	4.64

Analyzing the results, it can be seen that the CBR and JNN shown overall better results than the ARIMA model, but not as satisfactory as the other three neural networks. The RNN, GRU and LSTM models presented very close results at all horizons. For PH=2h the RNN model presented the lowest RMSE value, for PH=4h it was the GRU architecture and lastly, both the RNN and LSTM networks presented the same RMSE value for PH=12h.

Of the three models with the best results, the RNN is simpler and faster to train. For this reason, it was considered pertinent to present the plots of the patients for a better visualization of the results. The predictions for patient 116 are shown in Figure 5.2, while the plots for the remaining two patients are in Appendix B. Through these plots we realize that the model can satisfactorily predict future glucose values for 2h and 4h prediction intervals. The rise and fall of glucose can be anticipated, corresponding to our goal. Note that the initial portion of the graph that does not contain the yellow line corresponds to the lookback used as input. Regarding the results for the 12h prediction we can state that through the tables they seem satisfactory, but when analyzing the graphs we see that they are not so acceptable. These differences may be due to the fact that using a larger lookback than the two other PHs, uses fewer points to calculate the evaluation metrics in-

Table 5.8: Comparison of the performance for PH=12h – RMSE.

RMSE (mg/dL) - PH=12h							
Subject ID	**Trial No.**	**ARIMA**	**CBR**	**RNN**	**GRU**	**LSTM**	**JNN**
102	1	28.19	25.65	25.42	25.45	25.27	26.64
102	2	38.30	39.65	37.84	39.49	40.18	41.54
106	1	55.13	42.05	46.66	46.41	47.75	47.79
106	2	56.73	50.55	47.80	48.05	47.32	52.15
116	1	54.16	61.15	55.84	57.24	60.00	54.75
116	2	84.69	92.54	87.57	87.56	84.61	85.44
	Mean	52.87	51.88	50.19	50.70	50.19	51.39
	SD	17.59	21.18	19.21	19.10	18.05	17.77

Table 5.9: Comparison of the performance for PH=12h – MAPE.

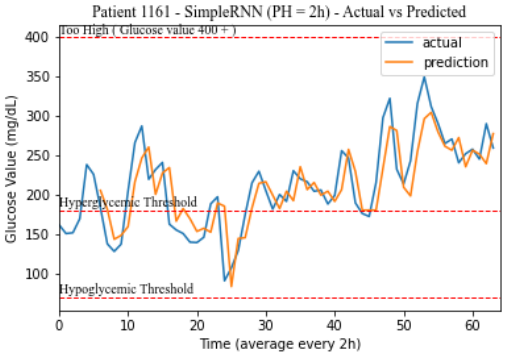
MAPE (%) - PH=12h							
Subject ID	**Trial No.**	**ARIMA**	**CBR**	**RNN**	**GRU**	**LSTM**	**JNN**
102	1	18.98	18.06	16.91	16.67	16.63	16.99
102	2	25.87	27.63	27.30	28.64	29.38	28.48
106	1	30.62	22.35	26.01	25.32	26.63	25.61
106	2	28.87	25.99	26.47	26.16	25.40	26.11
116	1	22.25	25.59	22.93	23.70	23.00	22.19
116	2	42.92	47.30	46.80	46.13	44.99	43.04
	Mean	28.24	27.82	27.74	27.77	27.67	27.07
	SD	7.62	9.24	9.21	9.00	8.69	8.01

ducing erroneously satisfactory values in the tables. Thus, the model should only be used for PH=12h with the knowledge that the results will not be as clinically relevant.

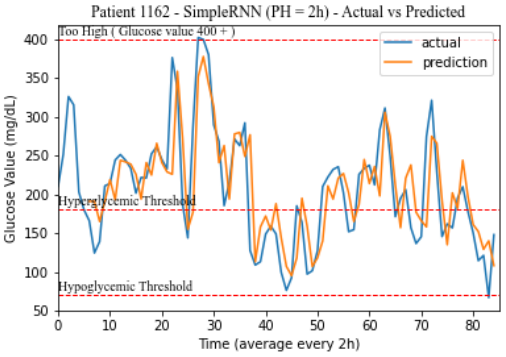
The results of this study are presented using two trials for each of the three test subjects. This allows us to gain insight into inter- and intra-subject variations. By analyzing the MAPE values we can get a better idea of these variations. Patient 102 shows the largest differences between trials for the 2h and 4h prediction horizons. There is an increase in the error by ∼10% and ∼23% from the first to the second trial, respectively. For the 12h prediction, patient 116 had a ∼22% higher average error in the second trial than in the first trial.

Clinical evaluation

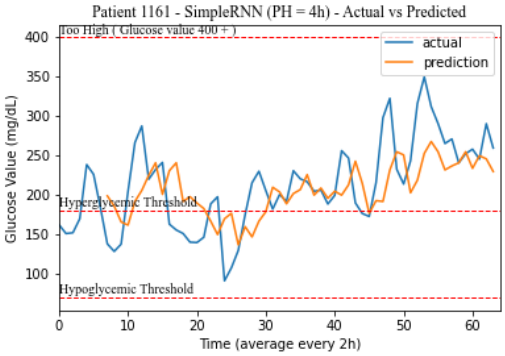
Despite the fact that the metrics mentioned above are crucial for comprehending the performance and prediction accuracy of different models from a regression analysis point of view, they are unable to identify the most significant outliers and do not offer any details about the clinical impact of prediction errors and their effects on medical treatment decisions. Therefore, we combined our assessment with Clarke Error Grid (CEGA) analysis to present a more full view of the models' performance.



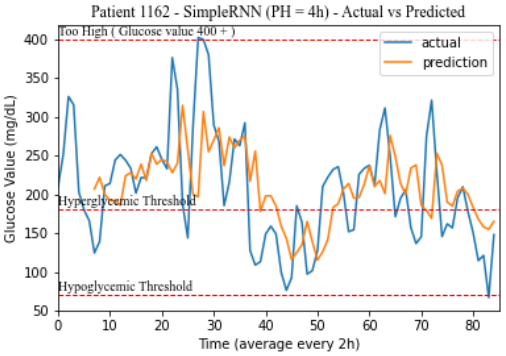
(a)



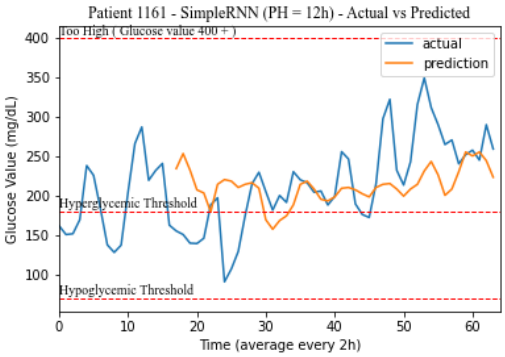
(d)



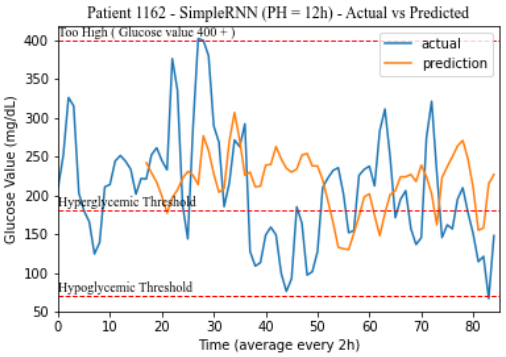
(b)



(e)



(c)



(f)

Figure 5.2: All graphs with the comparison between the actual (blue line) and predicted (yellow line) values for patient 116 when using the RNN model. a), b) and c) correspond to the prediction for the values of the first trial. d), e) and f) correspond to the prediction for the values of the second trial.

One of the most extensively used metrics for evaluating the clinical validity of blood glucose estimations is the CEGA. In actuality, it offers a clinical interpretation of the mapping between anticipated and actual blood glucose levels, which may be shown as a scatter plot with five distinct zones. Zones A and B are completely appropriate in terms of the therapeutic setting. D and E refer to the zones where prediction errors are most dangerous.

The comparison results for PH = 2h, 4h, and 12h for a percentage of predictions falling into zones A and B of the error grid analysis are in Tables 5.10, 5.11, and 5.12, respectively.

Table 5.10: Comparison of the performance for PH=2h – Grid error analysis, zones A and B. For each patient in both trials, the percentages of predictions falling into zones A and B, separated by a comma, are shown.

Zone A, zone B (%) - PH=2h

Subject ID	Trial No.	ARIMA	CBR	RNN	GRU	LSTM	JNN
102	1	67.90, 30.86	61.73, 37.04	69.14, 29.63	66.67, 32.10	66.67, 32.10	64.20, 34.57
102	2	42.50, 55.00	46.25, 52.50	42.50, 56.25	42.50, 56.25	38.75, 60.00	45.00, 53.75
106	1	52.5, 45.00	71.25, 28.75	68.75, 31.25	66.25, 33.75	68.75, 31.25	67.50, 32.50
106	2	53.16, 43.04	64,56, 34,18	68.35, 30.38	68.35, 30.38	67.09, 31.65	68.35, 30.38
116	1	60.34, 37.93	84,48, 15,52	82.76, 17.24	84.48, 15.52	86.21, 13.79	82.76, 32.91
116	2	44.30, 44.30	68,35, 26,58	68.35, 26.58	68.35, 26.58	68.35, 26.58	62.02, 32.91
	Mean	53.45, 42.69	66,10, 32,43	66.64, 31.89	66.10, 32.43	65.97, 32.56	64.97, 32.91
	SD	8.76, 7.33	11,44, 11,26	11.97, 11.86	12.28, 12.20	13.94, 13.81	11.12, 10.70

All models tested performed satisfactorily. More than 96% of the data in the 2h prediction horizon fall into zones A and B. It is noteworthy that the best results in this interval corresponded to the first trial of patient 106 which obtained an average of 84% of the values predicted by the models (except for ARIMA) in the zone with the best clinical outcome. For the 4h prediction horizon, the percentage of values in the clinically acceptable zones decreases to 95%. When considering a longer prediction horizon of 12h, about 94% of the predictions fall within the boundaries of zones A and B. Consistently with analytical assessment, the performance got worse when increasing further the prediction horizon. The ARIMA model presented, again, the worst results. For a prediction interval of 2h and 4h, the CBR model presented some of the best results together with the neural networks. For the 12h interval, RNN, LSTM, and JNN presented the best results.

Table 5.11: Comparison of the performance for PH=4h – Grid error analysis, zones A and B. For each patient in both trials, the percentages of predictions falling into zones A and B, separated by a comma, are shown.

Zone A, zone B (%) - PH=4h

Subject ID	Trial No.	ARIMA	CBR	RNN	GRU	LSTM	JNN
102	1	67.50, 32.50	57.50, 42.50	62.50, 37.50	60.00, 40.00	65.00, 35.00	65.00, 35.00
102	2	43.04, 54.43	39.24, 58.23	37.97, 59.49	45.57, 51.90	41.77, 55.70	45.57, 51.90
106	1	46.83, 48.10	54.43, 41.77	58.23, 40.51	54.43, 44.30	51.90, 46.83	51.28, 42.31
106	2	48.72, 43.59	57.69, 38.46	57.69, 39.74	57.69, 38.46	61.54, 32.05	61.40, 36.84
116	1	49.12, 47.37	63.16, 33.33	57.89, 42.10	56.14, 38.46	59.65, 40.35	42.31, 50.00
116	2	34.61, 48.72	47.44, 43.59	42.31, 50.00	42.31, 50.00	41.03, 51.28	52.07, 44.45
	Mean	48.30, 45.78	53.24, 42.98	52.77, 44.89	52.69, 43.86	53.48, 43.53	52.07, 44.45
	SD	9.89, 6.74	7.82, 7.62	9.16, 7.61	6.48, 4.86	9.40, 8.50	8.37, 6.78

5.1.4 Discussion

By taking into consideration the balance between performance and time cost for pre-train, the RNN model is chosen as the final model for this module. An associated complexity, and consequent computational burden, of the GRU and LSTM models do not contribute significantly to the improvement of the results.

Having two trials per patient allowed us to understand not only inter-subject differences but also intra-subject discrepancies. On the one hand, there are large differences in prediction between subjects (inter-subject variability), which suggests that personalized models, i.e., using the patient's own historical glucose data, would be able to achieve better results. On the other hand, since there was also large variability between trials for each patient (intra-subject variability), it could suggest the need for the algorithms to relearn the parameters as time progresses to overcome dynamic changes in the subject's glucose. Using only past and present glucose values as input data do not portray the complexity of Blood Glucose (BG) dynamics. Adding data from other sources and viable sensors that measure variables affecting the metabolic process could lead to optimized results. These information could be about food intake, insulin injections, exercise, and mental health-related parameters such as stress levels.

These experiments have a number of notable drawbacks. First, we are conscious of the big bias presented by the fact that the dataset size of 10 participants is regarded as small. Second, the dataset was not evaluated in any way as a rep-

Table 5.12: Comparison of the performance for PH=12h – Grid error analysis, zones A and B. For each patient in both trials, the percentages of predictions falling into zones A and B, separated by a comma, are shown.

Zone A, zone B (%) - PH=12h

Subject ID	Trial No.	ARIMA	CBR	RNN	GRU	LSTM	JNN
102	1	61.43, 38.57	61.43, 38.57	65.71, 34.29	65.71, 34.23	67.14, 32.86	60.00, 40.00
102	2	50.72, 47.83	44.93, 52.17	53.62, 44.93	52.17, 46.38	49.27, 49.27	43.48, 55.07
106	1	39.13, 56.52	57.97, 42.03	53.62, 46.38	55.07, 44.93	50.72, 46.38	50.72, 46.38
106	2	52.94, 42.65	64.71, 30.88	55.88, 38.23	61.76, 32.35	61.76, 32.35	58.82, 35.29
116	1	55.32, 42.55	44.68, 51.06	63.83, 31.91	57.48, 38.29	63.83, 34.04	53.19, 46.81
116	2	30.88, 54.41	29.41, 48.53	27.94, 57.35	26.47, 55.88	32.35, 52.94	27.94, 52.94
	Mean	48.40, 47.09	50.52, 43.87	53.43, 42.18	53.11, 42.02	54.18, 41.31	49.02, 46.08
	SD	10.30, 6.53	12.16, 7.56	12.35, 8.55	12.69, 8.03	11.77, 8.45	10.89, 6.85

resentation of the dynamics of the general population, i.e., the recordings made by the subset of individuals under free-living settings might not be a good indicator of the dynamics of the total T2DM population. The process for expanding the dataset with new participants should be investigated in greater detail in order to enhance the model.

The lack of studies in the literature on the prediction of glucose values for type 2 patients does not allow us to make comparisons with other researchers. Furthermore, as far as we know, no study on blood glucose prediction has been conducted for time horizons as long as the ones used. Kim et al. [39] constituted the only study we found on T2DM patients, which only uses historical glucose as input, and uses a PH=30min. With the increasing adoption of CGM devices by T2DM patients, more and more data will be collected, and future research could study glucose prediction for these patients.

5.2 Recommendation module

5.2.1 Rule generation

The Knowledge-Based Recommendation System (KBRS) built through an IF-THEN rule model was implemented by extracting knowledge from the guidelines in Appendix A. The collected guidelines were analysed and it was studied how to

incorporate the prediction module, considering the system goals and the project requirements, to define the input and output variables of the recommendation system.

Several input variables were stipulated. In Table 5.13 these are listed with their respective domains. The demographic variables of the patients are composed of sex and age. The patient's health status is mirrored through the Body Mass Index (BMI) value and the presence or absence of comorbidities (we consider only the most common ones in diabetic patients - Obesity, Hypertension and Dyslipidemia). Each measurement input is associated to a date and time. For glucose data, the current glucose value (*glucoseCur*), the predicted value for a given PH (*glucosePred*), obtained from the prediction module, and whether the future trend of the glucose value (*glucoseTendency*) is increasing or decreasing are used as inputs. About the patient's diet, the quantities of the following parameters ingested daily are taken into account: calories (*caloriesDaily*), carbohydrates (*carbsDaily*) and alcohol (*alcoholDaily*). The following convention was adopted to classify alcoholic drink consumption - 1 drink = 355 ml of beer, 148 ml of wine, or 44 ml of distilled spirits. Finally, the exercise-related variables consist of 3 vectors of size 7, where each position corresponds to one of the last 7 days. In each position the patient discriminates how many minutes of exercise were performed (*exerciseWeeklyDuration*), what type of exercise (*exerciseWeeklyType*) and with what intensity it was executed (*exerciseWeeklyIntensity*). It should be noted that for patients aged under 18 and over 65, only the minutes of physical activity performed per day in the last week are taken into account.

Table 5.13: List of variables used in the developed recommendation system where the domain of each one is described.

Input variable	**Domain**	**Input variable**	**Domain**
sex	'F', 'M'	*glucoseTendency*	1 - increase 2 - decrease
age	≥ 0	*carbsDaily*	≥ 0
BMI	≥ 0	caloriesDaily	[1000, 3000]kcal
comorbidities	'Obesity' 'Hypertension' 'Dyslipidemia'	*alchoolDaily*	≥ 0
dateTime	'dd/mm/yyyy HH:MM'	*exerciseWeeklyDuration*	≥ 0
glucoseCur	[20, 800]mg/dL	*exerciseWeeklyIntensity*	0 - No activity 1 - Moderate intensity 2 - High intensity
glucosePred	[20, 800]mg/dL	*exerciseWeeklyType*	0 - No activity 1 - Aerobic training 2 - Resistance training

For the output variables, at this point, we can only make inferences about some

variables where the possible recommendation is to indicate to decrease, maintain or increase the action in question. Recommendations can be about: the daily amount of carbohydrate intake, exercise weekly duration (in minutes), exercise daily duration (in minutes), exercise weekly frequency (in days), aerobic exercise weekly frequency (in days), resistance exercise weekly frequency (in days), daily amount of calories ingested and daily alcohol intake (*carbsDaily, exerciseWeeklyDuration, exerciseDailyDuration, exerciseWeeklyFreq, exerciseAerobicFreq, exerciseResistanceFreq, caloriesDaily, alcoholDaily*).

After having defined all input and output variables and their respective domains, the rules were formulated. Thirteen rules were created based on the guidelines presented in Appendix A. Each rule uses one or more input variables connected by the logical operator *and* and produces a recommendation on one of the output variables. This one, as previously indicated, can only correspond to decrease, maintain or increase the action present in the recommendation. The option to maintain is always initialized for all recommendations. By analyzing the input data and whether or not the rules are verified the recommendation can remain unchanged or can be assigned the value of increase or decrease as a recommendation.

In the implementation of the rules, in addition to the logical operator *and*, the following Python's built-in functions were used:

- *count()* returns the number of times an object appears in a list;
- *sum()* returns a number, the sum of all items in an iterable;
- *any()* returns *True* if any item in an iterable are true, otherwise it returns *False*;
- *all()* returns *True* if all items in an iterable are true, otherwise it returns *False*.

For rule R13 a specific function was created, called *check_exercise_pause_days()*, that returns *True* if there were two or more consecutive days in which no exercise was recorded, otherwise it returns *False*.

All the rules created for the recommendation module are described and represented in the implemented language in the table in Appendix C. Table 5.14 presents some of these rules as examples.

5.2.2 Discussion

These are the results obtained so far. However, the project is not yet finished and there are still some steps to be developed. In a future phase, a team of endocrinologists from Coimbra Hospital and University Centre (CHUC) will verify and complement these rules, especially with rules that use the values obtained by the

Table 5.14: List of some rules created with their description and representation in the language used (Python).

Rule ID	Rule description (Representation)
R01	IF an adult female patient drinks more than 1 drink a day THEN it is recommended to decrease daily alcohol intake (IF *sex* == 'F' and *age* > 18 and *alcoholDaily* > 1 THEN decrease *alcoholDaily*)
R02	IF an adult male patient drinks more than 2 drinks a day THEN it is recommended to decrease the daily alcohol intake (IF *sex* == 'M' and *age* > 18 and *alcoholDaily* > 2 THEN decrease *alcoholDaily*)
R03	IF an female patient with BMI greater than 25 kg/m2 consumes more than 1500 calories in a day THEN it is recommended to decrease the daily calories intake (IF *sex* == 'F' and *BMI* > 25 and *caloriesDaily* > 1500 THEN decrease *caloriesDaily*)
R04	IF an male patient with BMI greater than 25 kg/m2 consumes more than 1800 calories in a day THEN it is recommended to decrease the daily calories intake (IF *sex* == 'M' and *BMI* > 25 and *caloriesDaily* > 1800 THEN decrease *caloriesDaily*)

prediction module as input to create more personalized rules. This is the point of differentiation from existing recommendation models. Therefore, these corrections and new rules will be added to the existing rule set. It should be noted that the input variables that have not been used yet, correspond to some variables that will be in the rules developed by the endocrinologists. Therefore the model is already prepared to implement the rules that will be created.

Furthermore, this human expert evaluation by the healthcare professional will consist of a more complete and reliable evaluation of the developed recommendation system. So far, the system has been evaluated by creating hypothetical scenarios (creating a possible patient with the corresponding set of input data). The scenarios are designed to cover different situations for all aspects of our recommendations. In this way, it is verified that the rules are well evaluated and that recommendations are provided when needed. Several tests were performed in order to test all possible scenarios for the 13 rules already implemented.

5.3 Application programming interfaces

Based on these results, the best model developed for the prediction module and the rules designed for the recommendation module were incorporated to create the interface to be integrated into the project. This consists of a telemonitoring platform called SmartAL by Altice Labs. In Appendix D the interface is documented and all the functions created are described. The forecasting module has two functions, one to validate the inputs and another which, in the presence of valid inputs, runs the forecast at the discriminated PH (using the best model developed and previously trained). The recommendation module has three functions, one to validate the inputs, another, which receives these validated inputs, analyses them in order to

verify which of these do not comply with the stipulated rules and thus determines which recommendations to provide to the user. Finally, a function which helps define rule 13, verifying if there are more than two consecutive days in which the user has not exercised.

6

Conclusion and Future work

In this work two modules were developed within the POWER project (grant number POCI-01-0247-FEDER-070365). As in the rest of the document we will divide the conclusions by module.

In the prediction module, we addressed the problem of glucose level forecasting, using only Continuous Monitoring Device (CGM) data as input, for Type 2 Diabetes Mellitus (T2DM) patients. Our specific goal was to use a multi-patient training set to create a generalizable model for glucose level prediction that may be used to forecast future glucose levels for a new patient. This makes it possible to increase the models' usefulness even when they are just based on prior patient records. Another goal of the project was to integrate the values of these predictions into the recommendation module; to do this, long prediction horizons were established. Initially, horizons such as 2h, 4h, 12h, and 24h were chosen. However, it was found that due to the complexity of glucose dynamics (dependent on several factors and not only on the patient's CGM data history) this last option becomes unfeasible.

Through the results obtained, the three types of Recurrent Neural Networks (RNNs) obtained the most satisfactory results. Through a compromise between model performance and computational complexity, the RNN model was chosen as the final model. It is concluded that this implementation can be used achieving satisfactory results for the 2h and 4h forecast horizon. For its use in a 12h forecast horizon it should be known in advance that the results will not be the most favorable. Furthermore, we also concluded that the deep learning model algorithms got the highest results, which is agreement with the state of the art results. We used 3 random patients from the 10 available in the dataset to test the implemented algorithms. The global results of the 3 patients for the RNN model were: 34.82 mg/dL for Root Mean Square Error (RMSE) and 18.33% for Mean Absolute Percentage Error (MAPE) (PH=2h); 46.59 mg/dL for RMSE and 24.35% for MAPE (PH=4h); 50.19 mg/dL for RMSE and 27.74% for MAPE (PH=12h).

A contribution of this work is that we developed a prediction model for patients

with type 2 diabetes, whose existence in the literature is scarce. More studies are needed in this area to understand and improve models for these patients. Further research should be done in order to identify which prediction horizons are most useful for type 2 patients.

As future work, since machine learning models improve their classification with more data, it is important to increase the size of the dataset with more patients and preferably with records over a long period. One of the future steps of this project is to validate the implemented models on a dataset collected and provided by Coimbra Hospital and University Centre (CHUC). With this data, it is intended to incorporate some more features besides recording glucose values, such as carbohydrate intake and activity level. It is also important to make a better grid search on the implemented models and explore more deeply how much historical data on glucose levels should be used to estimate future values, to verify if it is possible to get better performances. In addition to this, the proposed method could also be tested on patients who are supervised for different periods to explore the consistency of the results and what the influences of physiological changes are.

Regarding the recommendation module, not all goals have been achieved yet, since the project is still under development. The model created so far uses rules extracted from guidelines provided by major international diabetes associations. All the rules developed were tested by creating hypothetical scenarios in order to understand if they were suggested when necessary and correctly. As mentioned before, in a future phase, a team of endocrinologists from the CHUC will verify and complement these rules. These health profissionals will have the important task of developing new rules that use the values obtained by the prediction module as input to create more personalized rules. So, a personalized model will be created, using the patient's own predicted values as the basis for the recommendations, with a high degree of confidence due to the validation made by the endocrinologist.

The future stages of this project, which will count on the partnership of Altice Labs and CHUC, will be crucial in validating and improving the modules developed. When completed, the Application Programming Interface (API) implemented in Altice's SmartAL remote management platform for diabetic patients will be updated.

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Appendices

A

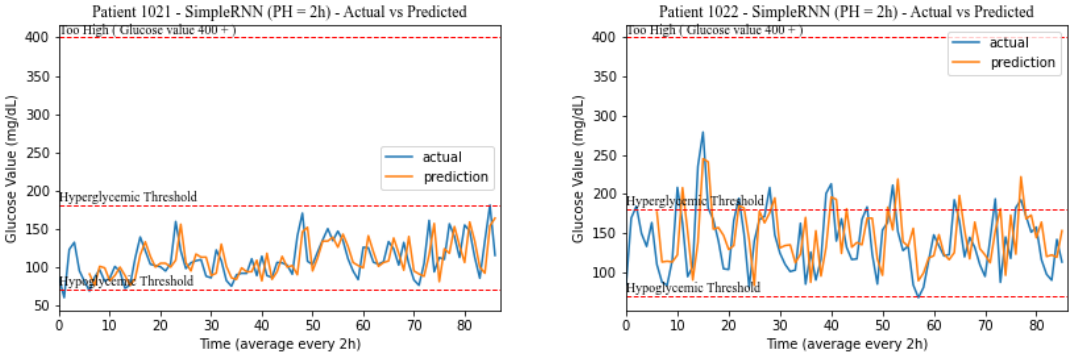
Guidelines from international diabetes-related associations

Table A.1: List of guidelines extracted from public documents made available by international diabetes-related associations that meet the requirements of this project.

Guideline	Sources
Physical Activity	
Children and adolescents with type 1 or type 2 diabetes or prediabetes should engage in 60 min/day vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week.	[30, 82]
Most adults with type 1 and type 2 diabetes should engage in 150 min or more of moderate-to-vigorous intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.	[3, 30, 35, 82]
Adults with type 1 and type 2 diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.	[3, 30, 35, 82]
Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance.	[30, 82]
Diet and Nutrition	
Weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit or provide 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, adjusted for the individual's baseline body weight.	[30]
For women, no more than one drink per day, and for men, no more than two drinks per day is recommended (one drink is equal to a 12-oz beer, a 5-oz glass of wine, or 1.5 oz of distilled spirits).	[30]

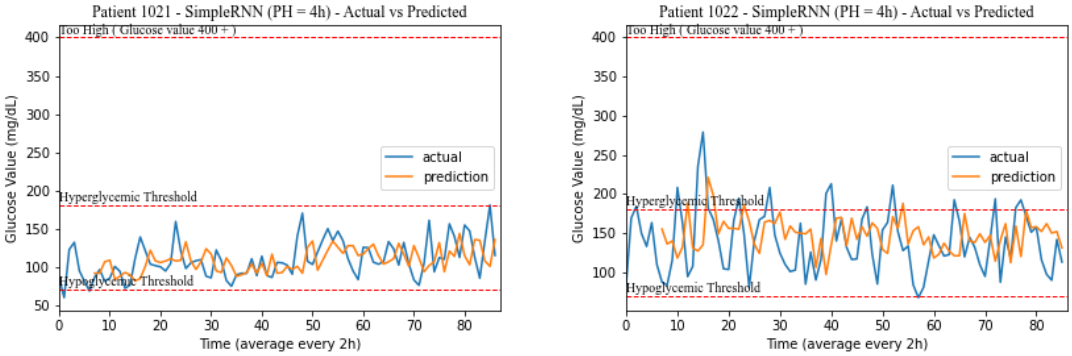
B

Graphs for all predictions using the RNN model for patients 102 and 106



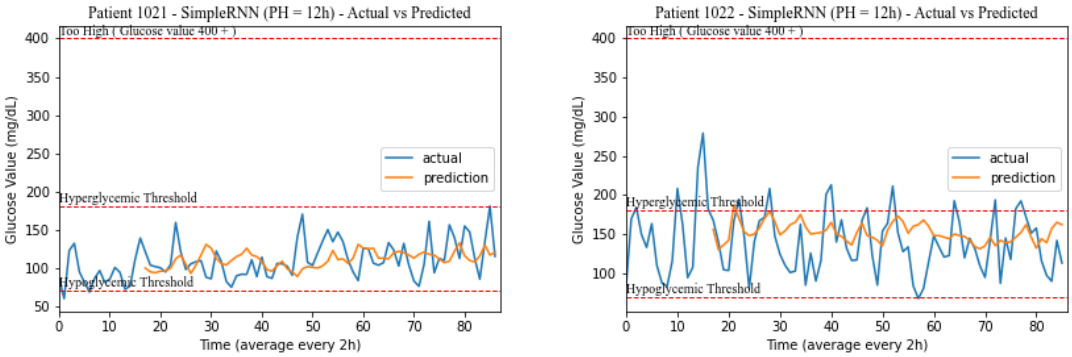
(a)

(d)



(b)

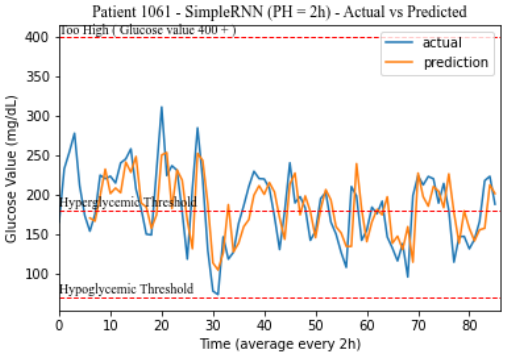
(e)



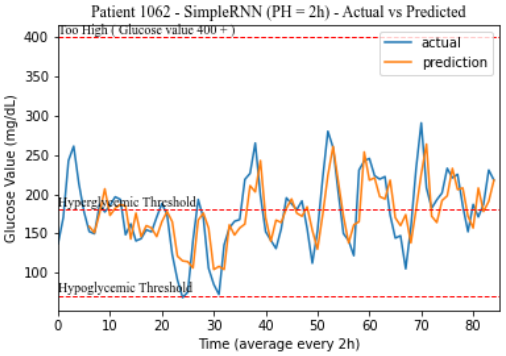
(c)

(f)

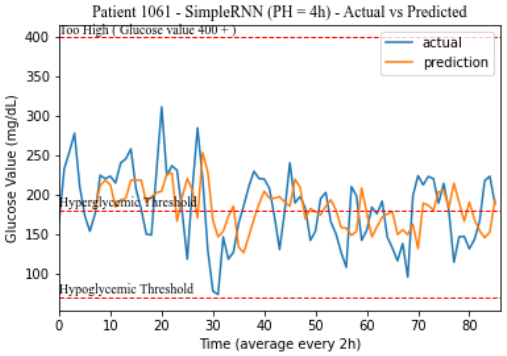
Figure B.1: All graphs with the comparison between the actual (blue line) and predicted (yellow line) values for patient 102 when using the RNN model. a), b) and c) correspond to the prediction for the values of the first trial. d), e) and f) correspond to the prediction for the values of the second trial.



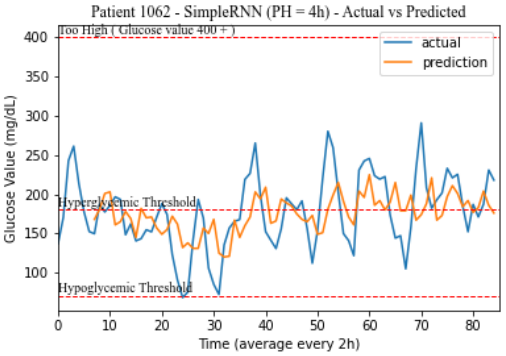
(a)



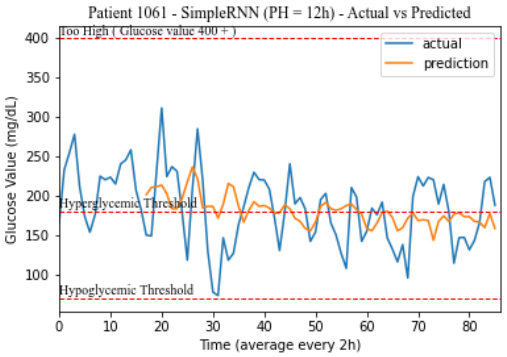
(d)



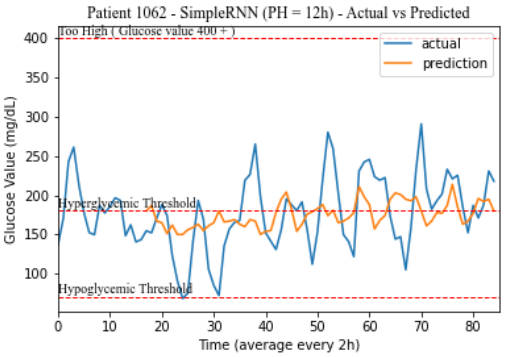
(b)



(e)



(c)



(f)

Figure B.2: All graphs with the comparison between the actual (blue line) and predicted (yellow line) values for patient 106 when using the RNN model. a), b) and c) correspond to the prediction for the values of the first trial. d), e) and f) correspond to the prediction for the values of the second trial.

C

List of all rules created for the recommendation module

Table C.1: List of all the rules created with their description and representation in the language used (Python).

Rule ID	Rule description (Representation)
R01	IF an adult female patient drinks more than 1 drink a day THEN it is recommended to decrease daily alcohol intake (IF *sex* == 'F' and *age* > 18 and *alcoholDaily* > 1 THEN decrease *alcoholDaily*)
R02	IF an adult male patient drinks more than 2 drinks a day THEN it is recommended to decrease the daily alcohol intake (IF *sex* == 'M' and *age* > 18 and *alcoholDaily* > 2 THEN decrease *alcoholDaily*)
R03	IF an female patient with Body Mass Index (BMI) greater than 25 kg/m2 consumes more than 1500 calories in a day THEN it is recommended to decrease the daily calories intake (IF *sex* == 'F' and *BMI* > 25 and *caloriesDaily* > 1500 THEN decrease *caloriesDaily*)
R04	IF an male patient with BMI greater than 25 kg/m2 consumes more than 1800 calories in a day THEN it is recommended to decrease the daily calories intake (IF *sex* == 'M' and *BMI* > 25 and *caloriesDaily* > 1800 THEN decrease *caloriesDaily*)
R05	IF an older patient does not perform at least two days of exercise per week THEN it is recommended to increase the amount of weekly exercise (IF *age* $\geq$ 65 and *exerciseWeeklyDuration*.count(0) > 5 THEN increase *exerciseWeeklyFreq*)
R06	IF an younger patient does not perform at least three days of exercise per week THEN it is recommended to increase the amount of weekly exercise (IF *age* $\leq$ 18 and *exerciseWeeklyDuration*.count(0) > 4 THEN increase *exerciseWeeklyFreq*)
R07	IF a younger patient performs physical activity lasting less than 60 min THEN it is recommended to increase the amount of daily exercise (IF *age* $\leq$ 18 and any((x ! = 0 and x < 60) or all(x == 0 for x in *exerciseWeeklyDuration*)) THEN increase *exerciseDailyDuration*)
R08	IF an adult patient performs moderate intensity physical activity without reaching 150 min per week THEN it is recommended to increase the amount of weekly exercise (IF 18 < *age* $\leq$ 65 and sum(*exerciseWeeklyDuration*) < 150 and *exerciseWeeklyIntensity*.count(1) > *exerciseWeeklyIntensity*.count(2) THEN increase *exerciseWeeklyDuration*)
R09	IF an adult patient performs high intensity physical activity without reaching 75 min per week THEN it is recommended to increase the amount of weekly exercise (IF 18 < *age* $\leq$ 65 and sum(*exerciseWeeklyDuration*) < 75 and *exerciseWeeklyIntensity*.count(1) < *exerciseWeeklyIntensity*.count(2) THEN increase *exerciseWeeklyDuration*)
R10	IF an adult patient in a week performs the same number of moderate and high intensity workouts without reaching 150 min per week THEN it is recommended to increase the amount of weekly exercise (IF 18 < *age* $\leq$ 65 and sum(*exerciseWeeklyDuration*) < 150 and *exerciseWeeklyIntensity*.count(1) = *exerciseWeeklyIntensity*.count(2) THEN increase *exerciseWeeklyDuration*)
R11	IF an adult patient in a week does not perform at least three aerobic workouts THEN it is recommended to increase the frequency of aerobic exercise (IF 18 < *age* $\leq$ 65 and *exerciseWeeklyType*.count(1) < 3 THEN increase *exerciseAerobicFreq*)
R12	IF an adult patient in a week does not perform at least two resistance workouts THEN it is recommended to increase the frequency of resistance exercise (IF 18 < *age* $\leq$ 65 and *exerciseWeeklyType*.count(2) < 2 THEN increase *exerciseResistanceFreq*)
R13	IF an adult patient does not exercise for more than two consecutive days THEN it is recommended to increase the weekly exercise frequency (IF 18 < *age* $\leq$ 65 and check_exercise_pause_days(*exerciseWeeklyDuration*) == *True* THEN increase *exerciseWeeklyFreq*)

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Interface definition of the glucose prediction and recommendation module

INTERFACE DEFINITION OF THE GLUCOSE PREDICTION AND RECOMMENDATION MODULES

Methods Listing

- predict_glucose
- validate_glucose_prediction_data
- recommendations_glucose
- validate_glucose_recommendation_data
- check_exercise_pause_days

predict_glucose

predict_glucose(patient_input, pred_horizon)

Returns an array of size 3, corresponding to the forecast at horizons 2h, 4h or 12h, respectively. When the parameters are invalid the array assigns all values -1. When the parameters are valid the array is represented in the first position by the forecast value corresponding to 2h after the last input value, in the second position by the forecast value corresponding to 4h after the last input value and in the last position by the forecast value corresponding to 12h after the last input value.

Parameters

patient_input : array_like

Array with input data. It is assumed that glucose values are acquired at a frequency of 5min (i.e., 1h of measurements corresponds to 12 glucose values).

pred_horizon: None or int

The prediction horizon argument can be empty (None) or can be an integer: 2, 4 or 12 (corresponding to 2h, 4h or 12h).

Returns

predictions: array_like

Array of size 3, corresponding to the forecast at horizons 2h, 4h or 12h, respectively.

error_code : int

Integer indicating the validity of the inputs (see table in *validate_glucose_prediction_data function*).

Notes

Tables 1 and 2 show the possible inputs that can be introduced depending on the desired forecasting horizon. There are inputs that allow the desired forecast with a lower confidence level in relation to the ideal input (which reaches the best results). When a specific prediction horizon is not introduced (None), the prediction is made taking into account the *patient_data* length.

For *pred_horizon* = 2, 4 or 12 (corresponding to 2h, 4h or 12h):

Desired prediction	Possible inputs with rising confidence level	Ideal input (highest confidence level)
2h	2h (24 values) 4h (48 values) 6h (72 values) 8h (96 values)	12h (144 values)
4h	4h (48 values) 8h (96 values)	12h (144 values)
12h	12h (144 values)	24h (288 values)

Table 1 - Possible inputs for the forecast horizons 2h, 4h and 12h.

If *pred_horizon = None*:

Input sent	Output achieved
2h (24 values) <= *len(patient_data)* < 4h (48 values)	2h prediction
4h (48 values) <= *len(patient_data)* < 12h (144 values)	2h and 4h prediction
len(patient_data) >= 12h (144 values)	2h, 4h and 12h prediction

Table 2 - Possible inputs for when no specific forecast horizon is introduced (None).

There is no issue with being sent a *patient_data* that is larger than the ideal input size.

Examples:

Invalid data entered (checked using the *validate_glucose_prediction_data* function): predictions = [-1, -1, -1].

Valid input data: regardless of the size of the input array, predictions is an array of size 3. This is represented in the first position by the forecast value corresponding to 2h after the last input value, in the second position by the forecast value corresponding to 4h after the last input value and in the last position by the forecast value corresponding to 12h after the last input value.

```
>>> predictions, error_code =
predict_glucose(patient_input, None)
[208.0, 169.0, 173.0], 0
>>> predictions, error_code =
predict_glucose([170, 95, '55'], None)
[-1, -1, -1], 202
>>> predictions, error_code =
predict_glucose(patient_input, 4)
[0, 124.0, 0], 0
```

In the first valid example it is assumed that *len(patient_input)* >= 24.
In the second valid example it is assumed that *len(patient_input)* >= 48.

validate_glucose_prediction_data

validate_glucose_prediction_data(patient_input, pred_horizon)

Assesses the validity of the *predict_glucose* function inputs, both the data array and the forecast horizon indication are evaluated. Values outside the allowable range are flagged and missing values are resolved where possible. In cases of too many missing values, invalid prediction horizons, or other errors described in **Table 3**, the function returns the value of *error_code* according to the error code that discriminates the situation.

Parameters

patient_input : array_like

Array with input data. It is assumed that glucose values are acquired at a frequency of 5min (i.e., 1h of measurements corresponds to 12 glucose values).

pred_horizon: None or int

The prediction horizon argument can be empty (None) or can be an integer: 2, 4 or 12 (corresponding to 2h, 4h or 12h).

Returns

error_code : int

Integer indicator of the validity of inputs (see **Table 3**).

patient_input : array_like

Input array with the changes made (if applicable).

Notes

The input is valid if it meets all the following conditions present in **Table 3**.

Parameter	*error_code*	Meaning
-	0	All data entered is valid.
pred_horizon	*101*	*pred_horizon* does not match one of the valid options (None, 2, 4 or 12).
patient_input	*201*	The input data contains NaN.
	202	Invalid value types in the input data (valid: int and float).
	203	For empty forecast horizon argument (None) or a 2h forecast, the entry must contain at least 24 values (2 hours).

	204	For a 4h forecast, the entry must contain at least 48 values (4 hours).
	205	For a 12h forecast, the entry must contain at least 144 values (12 hours).

Table 3 - Error codes and their meanings.

Examples

```
>>> error_code, patient_data = validate_glucose_prediction_data([170, 95, '55'], None)
202, [170, 95, '55']
>>> error_code, patient_data = validate_glucose_prediction_data(patient_input, None)
0, patient_input
```

In the valid example it is assumed that len(patient_input) >= 144.

recommendations_glucose

recommendations_glucose (sex, age, BMI, dateTime, comorbidities, glucoseCur, glucosePred_12h, glucoseTendency, carbsDaily, exerciseWeeklyDuration, exerciseWeeklyIntensity, exerciseWeeklyType, caloriesDaily, alcoholDaily)

Returns an array of size 8. When the parameters are invalid, the array assigns all values -1. When the parameters are valid, the array is represented by the values 1, 2 and 3 (corresponding to decrease, maintain and increase a given action, respectively) in all positions. Each position corresponds to the recommendation resulting from the evaluation of the input parameters. The recommendations correspond to, in order: carbohydrate intake, weekly duration in minutes of exercise, daily duration in minutes of exercise, weekly frequency in exercise days, weekly frequency in aerobic exercise days, weekly frequency in resistance exercise days, daily calorie intake and daily alcohol intake (carbsDaily, exerciseWeeklyDuration, exerciseDailyDuration, exerciseWeeklyFreq, exerciseAerobicFreq, exerciseResistanceFreq, caloriesDaily, alcoholDaily).

Parameters

sex: string

String referring to the user's sex. Should be inserted 'M' for male and 'F' for female.

age: int

Positive integer greater than zero referring to the age of the user.

BMI: float

Float greater than zero referring to the user's body mass index, expressed in kg/m2.

dateTime: string

String with information about the date and time of the measurements input. It must be in the format "dd-mm-yyyy HH:MM".

comorbidities: string ou None

String referring to the patient's comorbidities (the following pathologies can be entered: Obesity, Hypertension, Dyslipidemia). If there is more than one, separate with a comma. If it does not apply, it can be empty (None).

glucose_Cur: float ou int

Float or integer indicating the current glucose value in mg/dL.

glucosePred_12h: float ou int

Float or integer indicating the glucose value in mg/dL expected in a time frame = 12h.

glucoseTendency: int

Integer indicating the trend of glucose values. Must be entered 1 for an increasing trend and 2 for a decreasing trend.

carbsDaily: int

Integer indicating the amount of carbohydrates ingested on the current day, in grams.

exerciseWeeklyDuration: array_like

Array composed of 7 integers greater than or equal to zero, where each position corresponds to the duration (min) of physical exercise performed each day, for the last 7 days.

exerciseWeeklyIntensity: array_like

Array made up of 7 integers, where each position corresponds to the intensity of physical exercise performed each day, for the last 7 days. The integers that make up the array can take three values: 1 - moderate intensity; 2 - high intensity; or 0 - no physical exercise was performed.

exerciseWeeklyType: array_like

Array made up of 7 integers, where each position corresponds to the type of physical exercise performed each day, for the last 7 days. The integers that make up the array can take two values: 1 - performed aerobic exercise; 2 - performed resistance exercise; or 0 - no exercise was performed. In case the patient performs a training with both components on the same day, only one (the most predominant) should be registered.

caloriesDaily: int

Integer indicating the amount of calories ingested on the present day, in kcal.

alcoholDaily: int

Integer indicating the amount of alcoholic beverages drunk on this day (1 drink = 355 ml of beer, 148 ml of wine or 44 ml of distilled spirits).

Returns

recommendations: array_like

Array composed of 8 integers, where each position corresponds to the recommendation resulting from the evaluation of the input parameters. The recommendations correspond to, in order: carbohydrate intake, weekly duration in minutes of exercise, daily duration in minutes of exercise, weekly frequency in exercise days, weekly frequency in aerobic exercise days, weekly frequency in resistance exercise days, daily calorie intake and daily alcohol intake *(carbsDaily,*

exerciseWeeklyDuration,exerciseDailyDuration, exerciseWeeklyFreq, exerciseAerobicFreq,exerciseResistanceFreq,caloriesDaily, alcoholDaily).

error_code : int

Integer indicating the validity of the inputs (see table of the function *validate_glucose_recommendation_data*).

Notes:

The parameters *exerciseWeeklyIntensity* and *exerciseWeeklyType* only apply to patients aged 18 to 65.

The input parameter conditions for each rule (R01 - R13) are shown in **Table 4**. Some input parameters are not presented in the tables because they do not currently condition any rule. **Table 5** presents the results of the recommendations for each output parameter according to the input parameter conditions for each rule (R01 - R13).

Examples:

Invalid input data (checked using the *validate_glucose_recommendation_data* function): recommendations = [-1, -1, -1, -1, -1, -1, -1].

Valid input data: regardless of the input data, recommendations is an array of size 8. When the parameters are valid, the array is represented by the values 1, 2 and 3 (corresponding to decrease, maintain and increase a given action, respectively).

```
>>> recommendations, error_code =
recommendations_glucose('F', 50, 29.9, '16-08-
2022 17:42', None, 130, 120, 1, 44, [0, 65, 0,
77, 0, 25, 0], [0, 1, 0, 1, 0, 2, 0], [0, 1,
0, 2, 0, 1, 0], 33, 3)
[2, 2, 2, 2, 3, 3, 2, 1], 0

>>> recommendations, error_code =
recommendations_glucose('F', 50, 29.9, '16-08-
2022 17:42', None, 130, 120, 1, 44, [0, 0, 0,
77, 0, 25, 0], [0, 1, 0, 1, 0, 2, 0], [0, 1,
0, 2, 0, 1, 0], 33, 3)
[-1, -1, -1, -1, -1, -1, -1, -1], 103
```

Rule ID	sex	age	BMI	exerciseWeeklyDuration	exerciseWeeklyIntensity	exerciseWeeklyType	caloriesDaily	alcoholDaily
R01	F	>18						>1
R02	M	>18						>2
R03	F		>25.0				>1500	
R04	M		>25.0				>1800	
R05		>=65		exerciseWeeklyDuration.count(0) > 5				
R06		<18		exerciseWeeklyDuration.count(0) > 4				
R07		<18		any((x !=0 and x < 60) or all(x == 0 for x in exerciseWeeklyDuration))				
R08		>=18 AND <65		sum(exerciseWeeklyDuration) < 150	exerciseWeeklyIntensity.count(1) > exerciseWeeklyIntensity.count(2)			
R09		>=18 AND <65		sum(exerciseWeeklyDuration) < 150	exerciseWeeklyIntensity.count(1) = exerciseWeeklyIntensity.count(2)			
R10		>=18 AND <65		sum(exerciseWeeklyDuration) < 75	exerciseWeeklyIntensity.count(1) < exerciseWeeklyIntensity.count(2)			
R11		>=18 AND <65				exerciseWeeklyType.count(1) < 3		
R12		>=18 AND <65				exerciseWeeklyType.count(2) < 2		
R13		>=18 AND <65		check_exercise_pause_days(exerciseWeeklyDuration) == True				

Table 4 - Input parameter conditions for each rule (R01 - R13).

Rule ID	carbsDaily	exerciseWeeklyDuration	exercisDailyDuration	exerciseWeeklyFreq	exerciseAerobicFreq	exerciseResistanceFreq	caloriesDaily	alcoholDaily
R01								1
R02								1
R03							1	
R04							1	
R05				3				
R06				3				
R07			3					
R08		3						
R09		3						
R10		3						
R11					3			
R12						3		
R13				3				

Table 5 - Results of the recommendations of each output parameter according to the conditions of the input parameters for each rule (R01 - R13).

validate_glucose_recommendation_data

validate_glucose_recommendation_data (sex, age, BMI, dateTime, comorbidities, glucoseCur, glucosePred_12h, glucoseTendency, carbsDaily, exerciseWeeklyDuration, exerciseWeeklyIntensity, exerciseWeeklyType, caloriesDaily, alcoholDaily)

Evaluates the validity of the *recommendations_glucose* function inputs. In cases of invalid inputs or other errors described in the **Table 6**, the function returns the value of *error_code* according to the error code that discriminates the situation.

Parameters

sex: string
String referring to the user's sex. Should be inserted 'M' for male and 'F' for female.

age: int
Positive integer greater than zero referring to the age of the user.

BMI: float
Float referring to the user's body mass index, expressed in kg/m2.

dateTime: string
String with information about the date and time of the measurements input. It must be in the format "dd-mm-yyyy HH:MM".

comorbidities: string ou None
String referring to the patient's comorbidities (the following pathologies can be entered: Obesity, Hypertension, Dyslipidemia). If there is more than one, separate with a comma. If it does not apply, it can be empty (None).

glucose_Cur: float ou int
Float or integer indicating the current glucose value in mg/dL.

glucosePred_12h: float ou int
Float or integer indicating the glucose value in mg/dL expected in a time frame = 12h.

glucoseTendency: int
Integer indicating the trend of glucose values. Must be entered 1 for an increasing trend and 2 for a decreasing trend.

carbsDaily: int
Integer indicating the amount of carbohydrates ingested on the current day, in grams.

exerciseWeeklyDuration: array_like

Array composed of 7 integers greater than or equal to zero, where each position corresponds to the duration (min) of physical exercise performed each day, for the last 7 days.

exerciseWeeklyIntensity: array_like

Array made up of 7 integers, where each position corresponds to the intensity of physical exercise performed each day, for the last 7 days. The integers that make up the array can take three values: 1 - moderate intensity; 2 - high intensity; or 0 - no physical exercise was performed.

exerciseWeeklyType: array_like

Array made up of 7 integers, where each position corresponds to the type of physical exercise performed each day, for the last 7 days. The integers that make up the array can take two values: 1 - performed aerobic exercise; 2 - performed resistance exercise; or 0 - no exercise was performed. In case the patient performs a training with both components on the same day, only one (the most predominant) should be registered.

caloriesDaily: int

Integer indicating the amount of calories ingested on the present day, in kcal.

alcoholDaily: int

Integer indicating the amount of alcoholic beverages drunk on this day (1 drink = 355 ml of beer, 148 ml of wine or 44 ml of distilled spirits).

Returns

error_code : int

Integer indicator of the validity of inputs (**see Table 6**).

dateTime: timestamp

Timestamp referring to the date and time of the user's information entry, checked from the input string dateTime.

Notes

The input is valid if it meets all the conditions described in **Table 6**.

Parameter	*error_code*	Meaning
-	0	All data entered is valid.
sex	*10*	Does not match a valid string (valid: 'F' and 'M').

age	*20*	It does not correspond to a positive integer.
BMI	*30*	It does not correspond to a positive float.
dateTime	*40*	Does not match a string indicating date and time of measurement in 'dd/mm/yyyy HH:MM' format.
comorbidities	*50*	Invalid value types (valid: None and string).
	51	The string entered does not correspond to the possible options: Obesity, Hypertension, Dyslipidaemia.
glucoseCur	*60*	Does not match an integer or float >= 20.
glucosePred_12h	*70*	Does not match an integer or float >= 20.
glucoseTendency	*80*	Does not correspond to one of the valid options (valid: 1 and 2).
carbsDaily	*90*	Does not correspond to an integer >= 0.
exerciseWeeklyDuration	*100*	Value assigned None or the array is not of size 7.
	101	Incorrect value type in some position of the array (valid: int).
	102	Some position in the array does not correspond to positive values.
	103	For patients with 18 <= age < 65: when there is a position !=0 in the array exerciseWeeklyDuration there must be in the same position a value 1 or 2 in the arrays exerciseWeeklyIntensity and exerciseWeeklyType. When there is a 0 in the array exerciseWeeklyDuration, all 3 arrays must have a zero in the same position.
exerciseWeeklyIntensity	*110*	Value assigned None or the array is not of size 7.
	111	Incorrect value type in some position of the array (valid: int).

	112	Some position of the array does not correspond to a possible value (valid: 0,1 and 2).
exerciseWeeklyType	*120*	Value assigned None or the array is not of size 7.
	121	Incorrect value type in some position of the array (valid: int).
	122	Some position of the array does not correspond to a possible value (valid: 0,1 and 2).
caloriesDaily	*130*	It does not correspond to a positive integer.
alcoholDaily	*140*	Does not correspond to an integer >= 0.

Table 6 - Error codes and their meanings.

Examples

```
>>> dateTime, error_code =
validate_glucose_recommendation_data('F', 50,
29.9, '16-08-2022 17:42', None, 130, 120, 1,
44, [0, 65, 0, 77, 0, 25, 0], [0, 1, 0, 1, 0,
2, 0], [0, 1, 0, 2, 0, 1, 0], 33, 3)
datetime.datetime(2022, 8, 16, 17, 42), 0

>>> dateTime, error_code =
validate_glucose_recommendation_data('F', 50,
29.9, '16-08-2022 17:42', None, 130, 120, 1,
44, [0, 0, 0, 77, 0, 25, 0], [0, 1, 0, 1, 0,
2, 0], [0, 0, 0, 2, 0, 1, 0], 33, 3)
datetime.datetime(2022, 8, 16, 17, 42), 103
```

check_exercise_pause_days

check_exercise_pause_days (*exerciseWeeklyDuration*)

Checks if there were two or more consecutive days of no exercise. Used in R13 of the *recomendations_glucose* function.

Parameters

exerciseWeeklyDuration: array_like

Array composed of 7 integers greater than or equal to zero, where each position corresponds to the duration (min) of physical exercise performed each day, for the last 7 days.

Returns

check : boolean

Boolean indicator if there were two or more consecutive days when there was no physical exercise (True - if there were; False - if there were not).

Examples

```
>>> check_exercise_pause_days([0, 65, 0, 77,
0, 25, 0])
False

>>> check_exercise_pause_days([0, 0, 0, 77, 0,
25, 0])
True
```